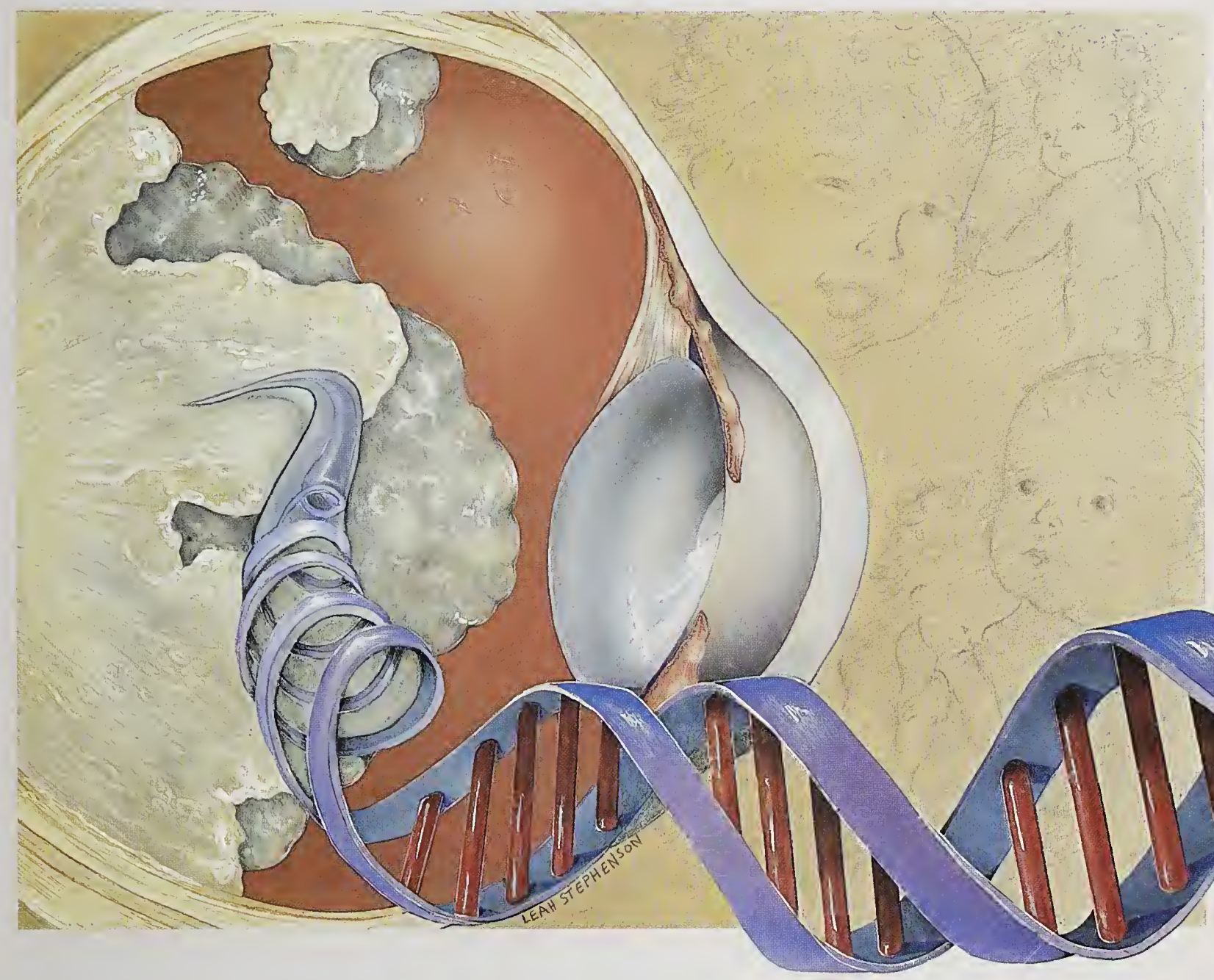
University of Toronto
MEDICAL JOURNAL
VOL. LXVI NO. 3



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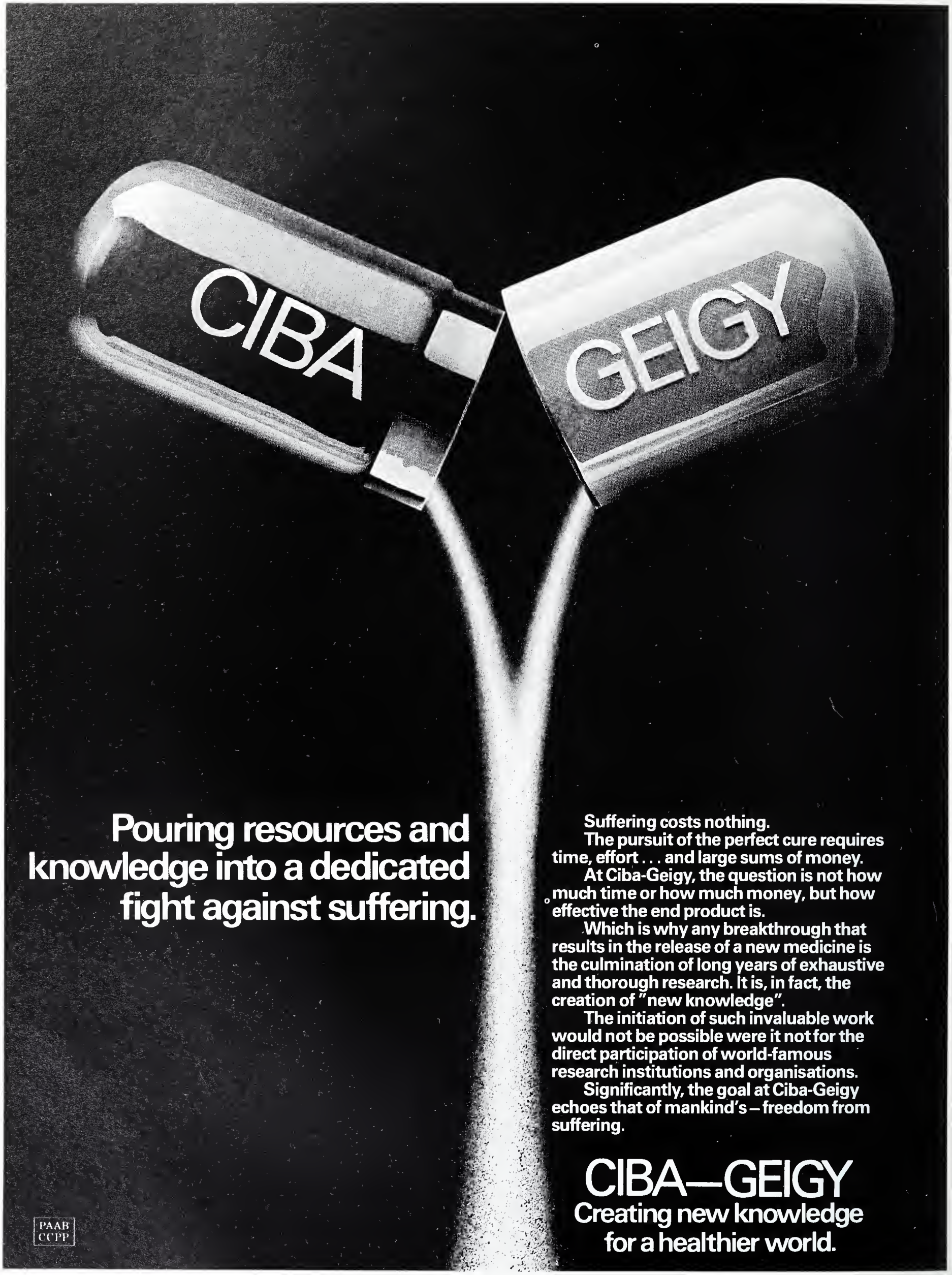
- Cardiac and Pericardial Calcification
- Soft-tissue Sarcoma Imaging
- Retinoblastoma Gene
- Pre-eclampsia
- Head-injured Patients
- Acute Abdomen



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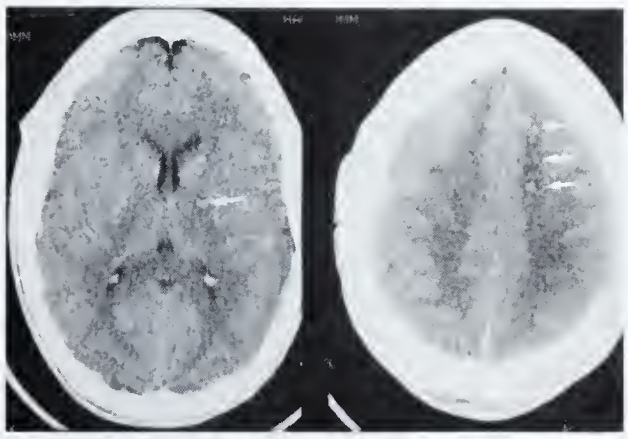

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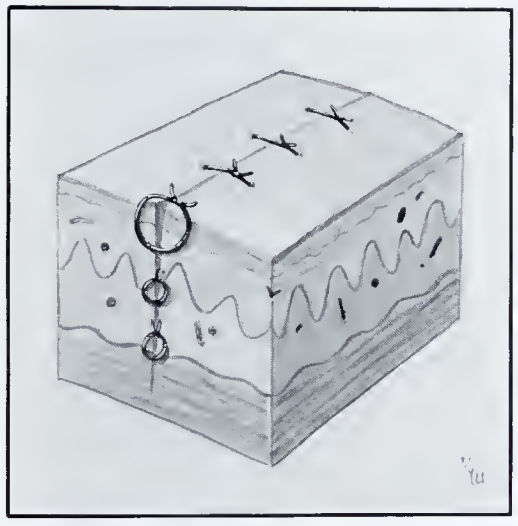

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Editorial

Michael J. Weinberg
Catherine Birt
Editors-in-Chief

Writing the editorial for the final issue always provides an opportunity to look back over the changes and progress that have occurred in the *Journal* during the year. One thing, of course, never changes. We always strive to publish high quality articles of interest to our readers. This year we have exercised particularly rigorous editorial standards. This issue alone contains basic work from fields as diverse as obstetrics, pathophysiology and molecular genetics as well as practical articles in the areas of radiology and plastic surgery. The excellence of the articles printed has been recognized by the R.I. Harris award for Orthopaedics, the Gladstone prize for the Neurosciences, and the second annual *University of Toronto Medical Journal* prizes for excellence in medical writing. The winners are listed inside this issue. This year, however, we have expanded our special feature section to include "Quick Dx", which tests readers' ability to make quick diagnoses from brief clinical presentations. Also new is "Impressions" through which students are encouraged to discuss unusual or special experiences in medicine. We have also departed from tradition by having more articles per issue and full colour covers on all three issues, making the *Journal* much more eye-catching. This has been primarily due to the generosity of our patrons.

Finally, we are, at the time of printing, working hard to get the *Journal* an even wider audience. We intend to send approximately 2000 copies to all the medical schools in Canada, and we are negotiating the inclusion of the *Journal* in the Medline computer literature search database. Both of these initiatives should bring the work of U. of T. medical students to the attention of many more people.

In conclusion, we would like to thank everyone who supported or participated in the production of the *Journal* this year. The *Journal* is a U. of T. tradition to be proud of, and we look forward to many more successful volumes.

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An Approach to Head-Injured Patients

Michael D. Cusimano, M.D., 8T4, Karim B. Nazarali, 9T0 and Steven Cusimano, U.W.O.*

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Abstract

Throughout their career almost all physicians will encounter patients with head trauma. This paper gives a general overview of head injuries. It includes a description of the pathogenesis of injury, the varieties of traumatic pathology, and the assessment and management of the head-injured patient.

Epidemiology

Four percent of the population will sustain an injury to the head each year. This includes injuries to the scalp, skull and brain and includes minor and major injuries. This is approximately equal to the incidence of peptic ulcer disease. Each year approximately 1% of the population will suffer a significant head injury and during this period there will be approximately 3,500 visits per 100,000 population to the emergency room because of head injury and, of these, 200 to 300 will be admitted to hospital.[1]

Head injury is predominantly a phenomenon of the young adult male, being twice as common in the male as the female.[2] The causes of head injury are variable according to age, sex, nationality, and whether the patient lives in an urban or rural situation. In children, falls and domestic accidents are most common, whereas, in adults, motor vehicle accidents, falls, and sporting activities are the most frequent associations.[1]

These facts highlight the important role that the physician can play in prevention of head injury. It is the physician's responsibility to encourage driver education, specifically regarding seatbelt use, alcohol abuse and adherence to speed limits. It has been shown conclusively that adherence to such preventive measures is effective in decreasing morbidity and mortality from head injury.[2] Of course, education in sports and domestic affairs is also of prime importance, especially in children.

Pathogenesis

Cerebral injury may be primary or secondary. The primary injury occurs at the time of the traumatic event, whereas the secondary event occurs sometime thereafter and is not directly due to the traumatic event itself.

Primary Injury

Primary injury is dependent on energy transfer between structures of different densities. The brain is deformable but not compressible and as such is prone to such energy transfers. The chief forces acting in traumatic situations are acceleration-deceleration forces with or without rotational forces. These forces are devastating because of shear stresses induced between bone and brain, between grey and white matter, between nerve fibers (Figure 1) and between vessels anywhere throughout the cranium. Such shear stresses can induce contusions, commonly in the frontal and temporal regions, or may induce hemorrhages because of stresses between bridging veins and intracerebral structures. Linear contact stresses may be responsible for skull fractures, scalp injuries and tearing of the meningeal artery leading to formation of epidural hematomas. The classical coup-contrecoup injury is attributed to acceleration-deceleration forces with lagging of the brain. An acute decompressive phenomena occurs when the brain accelerates into the skull that has become stationary.

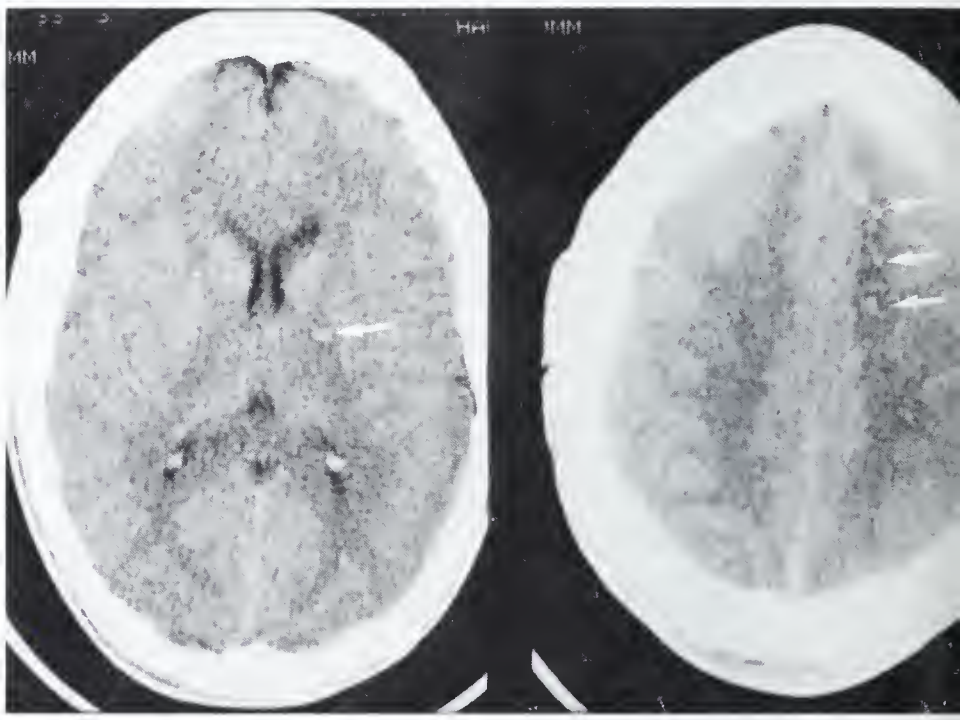

Figure 1: Diffuse Axonal Injury. CT scans of brain showing diffuse small hemorrhages (arrows) throughout the white matter caused by injury due to shearing forces.

The other major form of primary injury to the brain is penetrating trauma. These injuries can be classified as low-velocity or high-velocity injuries. The low-velocity injury usually causes only local damage whereas a high-velocity injury will cause local damage and waves of compression and decompression along with the tract of the missile, causing severe increases in intracranial pressure and diffuse damage.

Secondary Injury

The prevention of secondary injury is of prime importance to the care of the head-injured patient. One third of patients who die after being admitted to hospital were initially well enough to talk at one time.[3] These secondary events which cause death and disability can be treated, and therefore, recognition of the factors leading to them is of utmost importance.

In considering cerebral protection, one must always try to maximize supply of oxygen and glucose to the brain and minimize demands on the brain. This is achieved through gaining proper perfusion of oxygenated, glucose-carrying blood to the brain. Perfusion of the brain is dependent on cerebral perfusion pressure (CPP) which is equal to systemic blood pressure (BP) minus the intracranial pressure (ICP); i.e., **CPP = BP - ICP**. The intracranial pressure is proportional to the volume of the brain, plus the volume of the CSF, plus the volume of any blood within the brain and the volume of any space-occupying lesions; i.e., **ICP $\propto$ Volume (Brain+Blood+CSF+SOL)**. Therefore, a change in any one of these will change intracranial pressure and consequently will effect cerebral perfusion and the supply of nutrients to the injured brain.

In thinking of demand, one thinks chiefly about the metabolism of the brain. Fever and seizures are critical in determining the rate of cerebral metabolism; therefore, such factors must be alleviated as soon as possible.

Extracranial Factors

Secondary events can be categorized broadly as extracranial or intracranial events. Extracranial events can be remembered by listing the five H's (Hypoxia, Hypercarbia, Hypotension, Hyperpyrexia, and H_2O). The importance of oxygenation necessitates a patent airway and gas exchange. The "A" and "B" of airway and breathing must be insured in every head-injured patient. The importance of hypoventilation leading to hypercarbia lies in the fact that increasing partial pressures of carbon dioxide in the blood will lead to vasodilation and an increase in the volume of blood, thus leading to increased intracranial pressure, (see formula for intracranial pressure above). This may be fatal in someone with borderline intracranial hypertension.

In patients who are hypotensive, cerebral autoregulation is lost and therefore the perfusion of the brain becomes pressure passive. Any drop in blood pressure may lead to a drop in cerebral perfusion and thus compromise the supply of nutrients to the brain thus putting the brain at risk for secondary injury. Thus the "C" in the "ABC's", namely maintenance of adequate circulation, is critical.

Hyperpyrexia is an important factor in the determination of cerebral metabolic rate. An increase in body temperature of one degree centigrade is associated with a 15% increase in the metabolic rate of the brain.

Disturbances in water and electrolytes are due mainly to diabetes insipidus, SIADH, and iatrogenic causes. These may lead to increased cerebral swelling and thus increased intracranial pressure.

Intracranial Factors

Intracranial factors contribute to secondary injury by disturbing the volume-pressure relationship of the brain. As noted earlier, the intracranial pressure is proportional to the volume of the brain, volume of the CSF, and the volume of blood plus any volume of a space occupying lesion. The curve described by change in intracranial pressure with respect to a change in volume is exponential after a critical point (Figure 2). That is, the brain can accomodate to changes in volume up to a certain point (high compliance). Beyond this point a small change in volume will cause a large change in pressure and thus disturb cerebral perfusion, significantly altering the status of the patient.

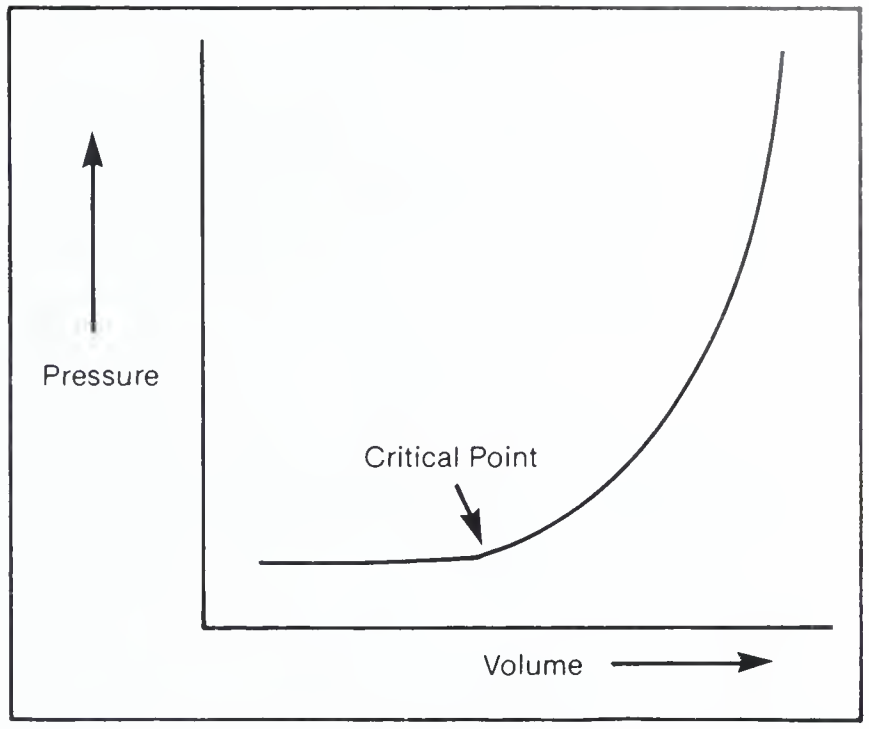

Figure 2: Relationship between intracranial pressure and intracranial volume. Intracranial pressure is kept relatively constant with increases in volume up to the critical point. Beyond the critical point, the cranium can no longer compensate for increases in volume and therefore small increases in volume leads to large increases in pressure. (Adapted from reference 7).

Several factors may increase the volume of the brain and thus increase the intracranial pressure. After trauma to the brain, the vessels become more permeable and this may lead to "vasogenic edema". Such vasogenic edema is characterized by increased extracellular water and can be treated by various osmotic agents such as Mannitol. Unfortunately, to this point the studies on Decadron have not shown any significant benefit in the traumatized patient.

Intracranial hemorrhages may develop as a secondary event and cause "late" deterioration in the patient due to brain shift, herniation and, ultimately, brainstem compression. Broadly speaking, intracranial hemorrhages can occur in two positions, extradural or intradural, with the latter being further subclassified as subdural, subarachnoid or intracerebral. Table 1 gives a classification of intracranial hemorrhages and their associated characteristics. Any of these may occur in association with a hemorrhage in another position. For example, a subdural hemorrhage may occur in association with an intracerebral hemorrhage.

Extradural hemorrhages classically occur in young patients who sustain trauma to the side of the head and are frequently associated with skull fractures of the temporal bone that lacerate the branches of the middle meningeal artery (Figure 3). The patient progresses

with a rapidly-deteriorating level of consciousness associated with a contralateral hemiplegia and ipsilaterally-dilated pupil (uncal herniation syndrome). The classical story of a lucid interval is present in not more than 15% of patients and one cannot depend on this as a diagnostic criterion.[4] These hematomas, in all but a few case reports, present as acute lesions. The prognosis for this lesion is excellent if diagnosed early and treated as soon as possible. Obviously, surgery is the major method of treatment in this type of hemorrhage.

Intradural hemorrhages more commonly present as late secondary events leading to worsened morbidity and mortality. Taken as a whole, the most common cause of subarachnoid hemorrhage is trauma but it is usually associated with other signs of significant brain or head trauma and is usually seen acutely. Subdural hematomas are usually due to an acute venous hemorrhage caused by rupture of cortical bridging veins and may be classified as acute (Figure 4) or chronic. The acute lesions have a worse prognosis because they are associated with primary brain injury as well. These patients may present with a rapidly expanding space-occupying lesion with a rostral-caudal herniation syndrome mimicking an extradural hematoma. Patients with chronic subdural hematoma are usually older and often have a history of ethanol abuse. They may present anywhere from 3 weeks to 3 months following a traumatic episode that may have been forgotten. Any neurologic signs may be present and formerly these hematomas were called the "great imitators" of neurosurgery. The signs and symptoms are often confused with those of cerebrovascular accident, encephalitis, or metabolic encephalopathy and tend to wax and wane.[5] The treatment here is evolving, but nonetheless, neurosurgical assessment is required.

Intracerebral hematomas are frequently associated with severe injuries, especially contusions and lacerations of brain. They often present acutely but may manifest themselves 3 to 5 days post-injury as a space-occupying lesion in the temporal lobe. They are generally associated with high morbidity and mortality but, if

Table 1

Intracranial Hemorrhages

Classification	Characteristics
1. Extradural	• Acute presentation • May have lucid interval • Uncal herniation syndrome • Skull fracture • Tear of middle meningeal artery • Lenticular shape on CT • Good prognosis if treated promptly
2. Intradural	
a) Acute Subdural	• Presents similar to extradural • Venous hemorrhage • Associated parenchymal brain injury • Crescenteric shape on CT • Poor prognosis
b) Chronic Subdural	• Delayed presentation • Trauma may be forgotten • Usually occur in elderly or alcoholic patients • Hypodense on CT
c) Intracerebral	• Presents as space occupying lesion • Associated with contusions, lacerations, other hemorrhages • Hyperdense on CT

Figure 3: Epidural Hematoma: CT scan of brain showing a hyperdense left epidural hematoma (arrows) in the classical lenticular configuration. There is also compression of the left ventricle and a midline shift of the brain.

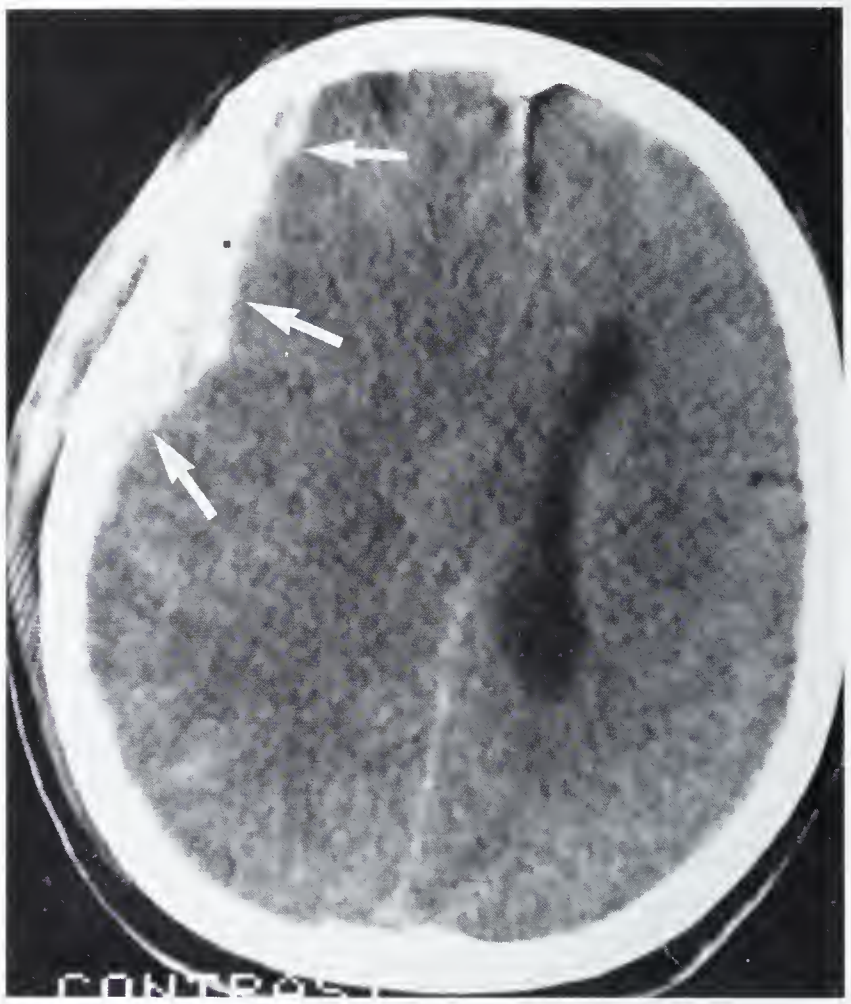

Figure 4: Acute Subdural Hematoma. CT scan of brain showing a hyperdense right acute subdural hematoma (arrows) in a crescenteric shape. There is also compression and shifting of normal brain structures.

managed quickly and intensively in a neurosurgical intensive-care unit, may have an excellent outcome.

Assessment and Diagnosis

Axioms

Several axioms should be remembered in the assessment of the head-injured patient in the emergency department. First, do not attribute a decreased level of consciousness to alcohol - a drunk patient may have an intracranial hematoma. Second, every patient with a head injury has a cervical spine injury until proven otherwise. Third, hypotension is not caused by head injury. (If there is a severe laceration of the scalp, the patient may sustain enough blood loss to cause hypotension. In the patient less than a year old with a skull fracture, the patient may sequester enough blood to drop his hemoglobin. Children with hydrocephalus also have more room for expansion in any intracranial hemorrhage and may also experience hypotension from the head injury. But these are all rare exceptions and, in general, the axiom of hypotension not being caused by the head injury can be held to be true). Fourth, lumbar puncture has no place in the management of the acute head-injured patient.

Initial Evaluation

The initial evaluation can be categorized into six special areas: resuscitation, mini-history, mini-physical, general physical, neurologic exam and special tests (Table 2). Resuscitation and maintenance of the ABC's of life support are the most important aspects of management. As noted previously, any compromise of airway, breathing or circulation in a traumatized patient may lead to secondary changes within the head and cause fatal brain herniation or worsening of a severe neurologic deficit. A mini-history concerning the head injury is of utmost importance and can be taken following resuscitation. The history should differentiate a true head injury from an injury secondary to a fall due to another cause. The circumstances leading to the injury and the temporal profile of neurologic status should be obtained. In addition, significant past history

Table 2

Components of The Initial Evaluation

1. Resuscitation
   - Maintenance of the ABC's to prevent 2°injury
2. Mini History
   - 1° or 2° injury?
   - How and when did it occur?
   - Neurologic status at scene?
   - How has it changed?
   - Other information
3. Mini Physical
   - Assess other major life-threatening injuries
4. General Physical
   - Chest
   - Abdomen
   - Extremities
   - Back
5. Neurological Exam
   - Level of consciousness
   - Head & Neck
   - Eyes
   - Brainstem function
   - Motor examination
   - Sphincters
6. Special Tests
   - X-rays
   - Arterial blood gases
   - Drug screen
   - Electrolytes

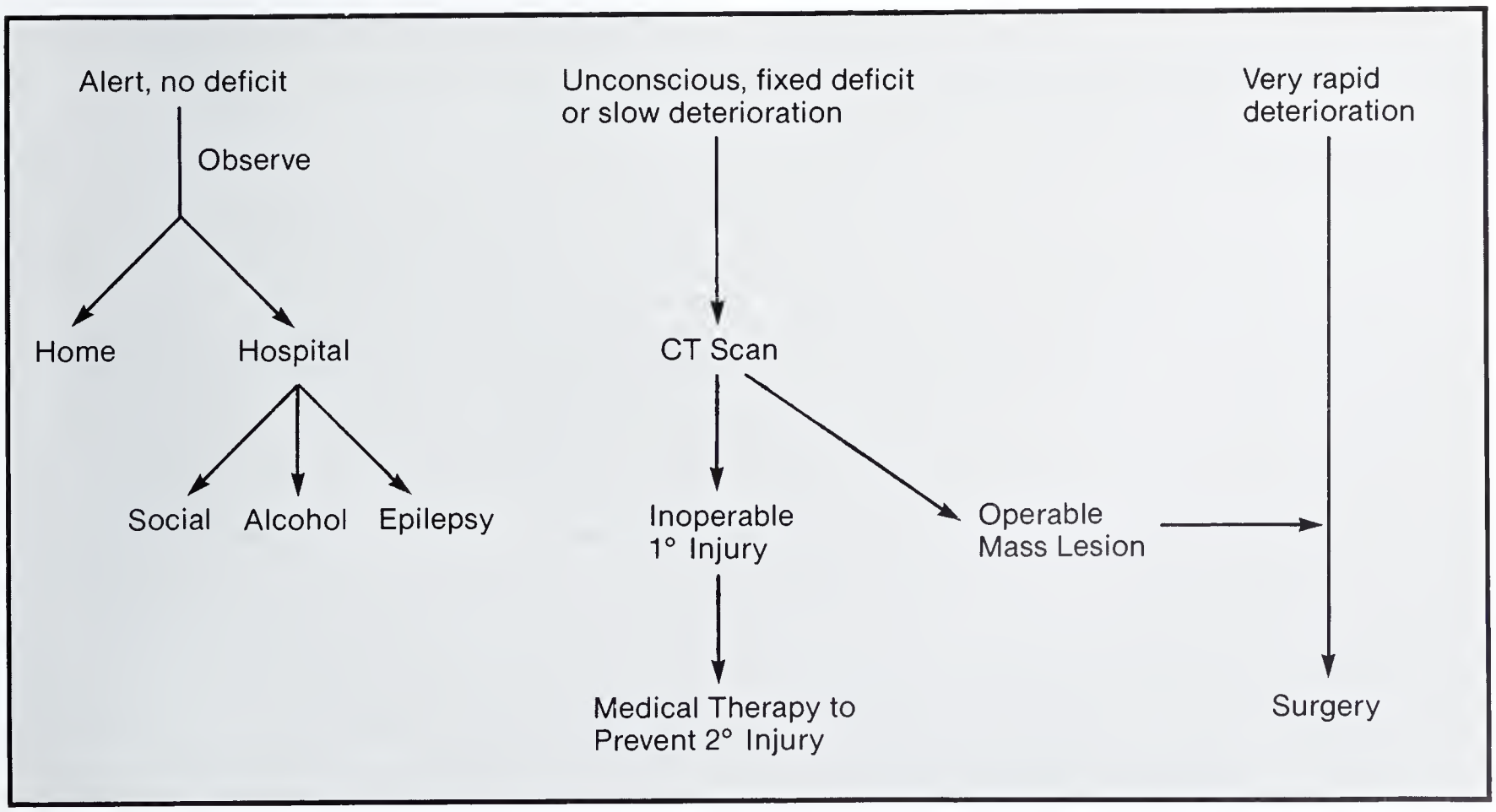

Figure 5: Quick Decisions. General approach in deciding management plans based upon the condition of the patient.

or other information (e.g. medications, allergies, etc.) that is important in the management of the patient should be determined. In conjunction with the resuscitation, a quick mini-physical exam is done to assess the ABC's. Next, a general physical exam is performed, usually in concert with a neurological exam. The latter should include six critical areas. These are assessments of the level of consciousness, the head and neck, the eyes, other brainstem functions, a motor examination, and a sphincter examination.

Level of Consciousness: The level of consciousness can be quickly evaluated using the Glasgow Coma Scale developed by Jennet and Teasdale.[1] This involves an assessment of eye opening, best verbal response and best motor response, and grades them on a cumulative 15-point scale. This scale has been shown to be valid, easy to perform and has good interobserver reliability.

Head and Neck: Examination of the head and neck is carried out first to rule out any evidence of direct penetrating trauma or deformities of the skull or spine. Findings such as racoon eye or battle sign will suggest a basal skull fracture. This may be associated with a CSF rhinorrhea or otorrhea. The tympanic membranes must be examined to rule out any hemotympanum. Quick assessment of facial fractures is performed by manual palpation and assessing if there is any movement of the maxilla or jaw with respect to the cranial skeleton.

Eyes: Pupillary size and reactivity, ocular position and movement should be assessed and recorded. Dysconjugate eye movements are more indicative of a structural rather than a metabolic lesion. If a cervical spine fracture has been ruled out, doll's eye testing can be performed. If the status of the cervical spine is uncertain, caloric testing should be done. Any movement of the eyes suggests that brainstem function still exists. The fundi are then examined for evidence of increased intracranial pressure; however, papilloedema may take up to 24 to 48 hours to develop and the absence of such does not rule out significantly-increased intracranial pressure.

Brainstem Function: Other brainstem functions are examined. Vital signs and respiratory pattern may suggest a Cushing response (systolic hypertension, bradycardia, bradypnea). Cheyne-Stokes breathing suggests bilateral hemispheric lesions or upper brainstem dysfunction. Corneal reflexes, gag and cough reflexes are also assessed.

Motor Examination: Motor examination is then performed to assess posturing, responses to pain, tone, reflexes and plantar responses in the patient.

Sphincters: Examination of anal sphincter tone, reactivity, and reflexes is performed to assess spinal cord function.

If the patient is cooperative enough, a sensory and quick cerebellar examination are also performed but these are usually not essential in the emergency management of a significantly head-injured patient.

As all the above-mentioned examinations are taking place, special tests are ordered as required. These may include complete blood count, arterial blood gases, electrolytes, drug screens (including ethanol), x-rays (minimum of C-spine, chest, pelvis) and other tests such as blood cross match, etc.

Management

Management of the head-injured patient initially requires a few quick decisions regarding the patient's condition, and then, based on these, provision of specific treatment (Figure 5). If the patient is completely alert without evidence of any neurological deficit on the initial exam, and is otherwise well, the patient should be observed either at home, if the social circumstances permit, or within the hospital. If the patient is unconscious and has a fixed deficit or demonstrates a slow deterioration, a CT scan should be performed. A CT scan may reveal a primary injury that is inoperable, so care is then directed to prevent secondary injuries. However, the CT scan may reveal a mass lesion which requires urgent neurosurgery. The third broad category are those patients showing such a rapid deterioration in their level of consciousness and neurologic function as to require immediate surgery with bypassing of the CT scan.

Scalp and Skull

Most scalp injuries are minor and all that is required is that they be cleaned, irrigated and debrided. Skull injuries should be assessed by placing a gloved-sterile hand into the wound and palpating the skull for any fracture. The clinical status of the patient may indicate underlying brain injuries as well. If the scalp laceration is severe enough, it may require rotating flaps or grafts performed by a plastic surgeon.

Recognition of skull injuries is dependent on clinical assessment and x-ray examination. Fractures are categorized into those of the vault and those of the base. First, fractures tend to occur in non-anatomical positions as opposed to natural vascular and suture markings. Sutures reveal a straighter inner table line and a jagged outer line corresponding to the outer table. Vessel markings due to venous structures occur in the diploic space, may be star shaped, and most commonly appear in the posterior parietal or anterior frontal region. Fractures are also straighter and more jagged than markings and have a sharper boundary. They may be branching at erratic angles and their calibre does not decrease as one goes along the fracture line. Indeed the calibre may change along the fracture line if it is opposed to the natural anatomical markings which show a natural dimunition in their calibre. Skull fractures may occassionally be radiodense because of superimposed pieces of bone caused occassionally by depressed fragments; however, there is usually no sclerosis around acute fractures. Fractures tend to go through foramena rather than beginning or ending at a foramen. It should be noted that basal skull fractures may be difficult to diagnose and these diagnoses are more often based on clinical signs such as racoon eyes or CSF otorrhea.

The value of a skull x-ray is controversial. In places where CT scanning and immediate neurosurgical care

Table 3

General Indications for X-ray Examination, for Admission to Hospital, and for Neurosurgical Consult in the Head-Injured Patient[6]

Indications for skull x-ray

1. Loss of consciousness or amnesia at any time.
2. Presence of neurologic symptoms or signs.
3. CSF or blood from the nose or ear.
4. Suspected penetrating injury.
5. Scalp swelling or laceration.

Indications for admission to hospital

1. Confusion or other depression of the level of consciousness at the time of examination.*
2. Skull fracture.
3. Patient with neurologic symptoms or signs.
4. Difficulty in assessing the patient. This includes patients who have a history of ethanol intake or epilepsy or other medication which may alter level of consciousness.
5. The lack of a responsible adult to supervise the patient and any other social problems associated with the patient.

Indications for a neurosurgical consult

1. Fractured skull with any of the following: confusion or decreased level of consciousness, one or more seizures, any other neurological signs or symptoms.
2. Coma continuing after primary resuscitation.
3. Decreasing level of consciousness.
4. Confusion or other neurologic disturbance persisting more than 8 hours.
5. Depressed skull fracture or basal skull fracture.
6. Penetrating injury.

* A patient with brief amnesia but full recovery at the time of examination is not necessarily a sufficient indication for admission to hospital in itself.

is not available, skull x-rays may indeed be of significant help in the management of a head-injured patient.

Brain

The specific management of brain trauma is directed against minimizing the agents responsible for the secondary injury process. The maintenance of airway, breathing and circulation are of utmost importance in preventing and treating secondary events as highlighted earlier. Intubation and hyperventilation of the patient, to ensure oxygenation and to prevent hypercarbia, is often all that is required to decrease intracranial pressure. Placing the patient in the head-up position will decrease venous back-pressure. If the deterioration is rapid or the initial measures have failed, treatment with osmotic agents such as Mannitol, given at a dose of 1 gram per kilogram, may be beneficial. There is some evidence that Lasix may add a cytoprotective element to this treatment and will prevent the initial increase in the intravascular volume phase seen with Mannitol. It should be noted that steroids and the use of barbiturates in the trauma situation have not been shown to be of benefit.

If one is faced with a situation of a rapidly-deteriorating patient with a dilated and fixed ipsilateral pupil, emergency surgery may be indicated by either a neurosurgeon or, if this is not available, by the primary surgeon or care giver. This would involve the insertion of burr holes, with or without the formation of a small craniotomy or craniectomy. The initial burr hole would be performed in the temporal area of the skull on the side of the dilated pupil, two finger-breadths posterior to the orbital margin and one to two finger-breadths superior to the zygomatic arch. If this is unsuccessful, the second burr hole is made approximately 3 to 4 centimeters off the midline on the coronal suture and a third burr hole over the parietal fossa can be made if necessary. In general, these extreme measures are not necessary because medical management is usually sufficient to buy the time necessary to obtain expert neurosurgical care.

As general guidelines, Table 3 identifies the indications for patients who require x-ray examination, hospital admission and those who require neurosurgical consultation.

Prognosis

Prognosis after head injury is dependent upon the severity of the primary injury, associated injuries, the age, and pre-morbid medical status of the patient. An elderly patient with the same injury as a younger patient will have a higher morbidity and mortality.[5] This is due to the higher incidence of medical complications and increased frequency of development of intracranial mass lesions in the aged. Table 4 summarizes the main prognostic factors.

Table 4

Prognosis in Severe Head Injuries*

Factor	Poorer Prognosis	Better Prognosis
Age	Old Age	Youth
Glasgow Coma Scale	< 7	> 7
Pupillary Light Reflex	Fixed, dilated pupil	Pupil constricts
Caloric Testing	Eyes do not deviate	Eyes deviate
Motor Response to Noxious Stimuli	Posturing	Localizes stimulus

*Adapted from reference 5.

Acknowledgements

The author wishes to acknowledge Professor R. Fleming, Division of Neurosurgery, Toronto Western Hospital, for his undergraduate and postgraduate teaching.

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The Comparative Value of the Bone Scan and the CT Scan in Determining Bone Involvement by Soft-Tissue Sarcoma

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Abstract

In thirteen patients with a soft-tissue sarcoma, radionuclide bone scans were 54% accurate in evaluating the presence or absence of involvement of contiguous bone by the tumour. Computed tomograms were found to have a similar accuracy of 58%. As determination of the relationship of the soft-tissue tumour to bone is an important part of the accurate anatomical staging that is required to select appropriate surgical management, a more accurate modality is needed.

Soft-tissue sarcomas (STS) are potentially lethal mesenchymal tumours that originate in the nonvisceral connective tissues.[1-4] They account for approximately 1% of all malignant tumours in adults and are most commonly found in the extremities.[1-3,5]

Adequate surgical resection is the most important factor in the local control of STS.[2,6-8] Determination of the anatomical relationship of the tumour and its surrounding soft-tissue reactive rim (pseudocapsule) to adjacent structures allows the surgeon to plan adequate resection margins while preserving maximal function.[9-13] Thus, accurate localization of tumour is crucial in developing an appropriate operative approach.

Physical examination, plain radiography, angiography, bone scanning, computed tomography (CT) and magnetic resonance imaging (MRI) are all utilized in the anatomical staging of STS.[12,14,15] As sarcomas often are found deep to the investing fascia of the extremity, they are relatively inaccessible to palpation. Reliance on imaging modalities is therefore necessary to delineate the relationship of the tumour to adjacent structures.

Figure 1: Surgical removal of soft-tissue sarcoma from thigh.

Of all imaging modalities widely used in the past, CT has proven to be the most accurate in delineating the anatomical location of STS.[5,8,12,14,16,17] However, in certain circumstances, other imaging modalities add unique information (for example, bone scanning in the detection of early skeletal metastasis from STS).[16] In some reports, bone scanning has been found to be superior to CT in the determination of bone involvement by soft-tissue tumour.[10,14] This study reevaluates the role of CT and bone scanning in the determination of bone involvement by adjacent tumour in a group of patients where bone involvement was a critical issue in management.

Materials and Methods

From May 1986 to December 1987, forty-nine patients with STS were evaluated by the Orthopaedic Oncology service at St. Michael's Hospital. Only those patients who had had preoperative bone and CT scans as well as definitive removal of the STS by the Oncology service were considered for inclusion in the study. By these criteria sixteen patients were excluded. Of the remaining thirty-three patients, clinical examination indicated that in thirteen cases the tumour's relationship to bone was critical in planning surgical management. These thirteen patients comprised the basis for this study (Table 1).

Bone Scanning

A routine whole body bone scan with Technetium 99m-labeled methylene diphosphonate was acquired. Anterior and posterior views were taken in all patients. In some patients, additional images of the area of interest were obtained. All scans were reviewed retrospectively by Nuclear Medicine specialists for the study. The

Table 1
Pathological Diagnosis of Soft-Tissue Sarcoma

Malignant Fibrous Histiocytoma	3
Spindle Cell Sarcoma	3
Alveolar Soft Part Sarcoma	1
Clear Cell Sarcoma	1
Liposarcoma	1
Leiomyosarcoma	1
Myxoid Soft-Tissue Chondrosarcoma	1
Rhabdomyosarcoma	1
Undifferentiated Sarcoma	1

bone scan was considered positive for bone involvement if there was an increase in tumour uptake in the bone adjacent to the tumour or when tumour uptake could not be distinguished from bone. The scan was considered negative for bone involvement if there was no abnormal activity in the scan or when a plane of normal tissue separated tumour activity from bone.[10,11]

Computed Tomography

Twelve of thirteen CT scans were available for retrospective review by Radiology specialists. One scan could not be located, and thus was unavailable for review. The scan was considered positive for bone involvement if the tumour made contact with bone or was within five mm of bone. Bone was considered uninvolved if more than five mm of normal tissue separated tumour from bone.[10]

Anatomical and Pathological Correlation

In all patients, pathology and operative reports were available, allowing determination of the anatomical relationship of the tumour to the bone. In ten of thirteen cases, all resection margins were negative for tumour cells, allowing complete determination of the relationship of the tumour to bone. In three cases a resection margin was considered to be involved by tumour cells (i.e., an incomplete margin). In one of these patients, an incomplete margin was necessary to preserve a major nerve. In another of these patients, an incomplete margin was necessary to preserve a major vessel. No incomplete resection margin was adjacent to bone by surgical observation.

All resected specimens were evaluated according to a prospective pathological protocol. In general, Hadju's definition of a microscopic positive margin was accepted, i.e., tumour cells approaching within one-half of a 10x microscopic field (one mm) of the resection margin constituted a positive margin.[18] However, in the case of a margin approximating bone, presence of tumour cells within five mm of the margin was considered to represent bone involvement since the dissection techniques necessary to remove soft-tissue from bone are more likely to result in wound contamination than the technique used in dissecting through soft-tissue.

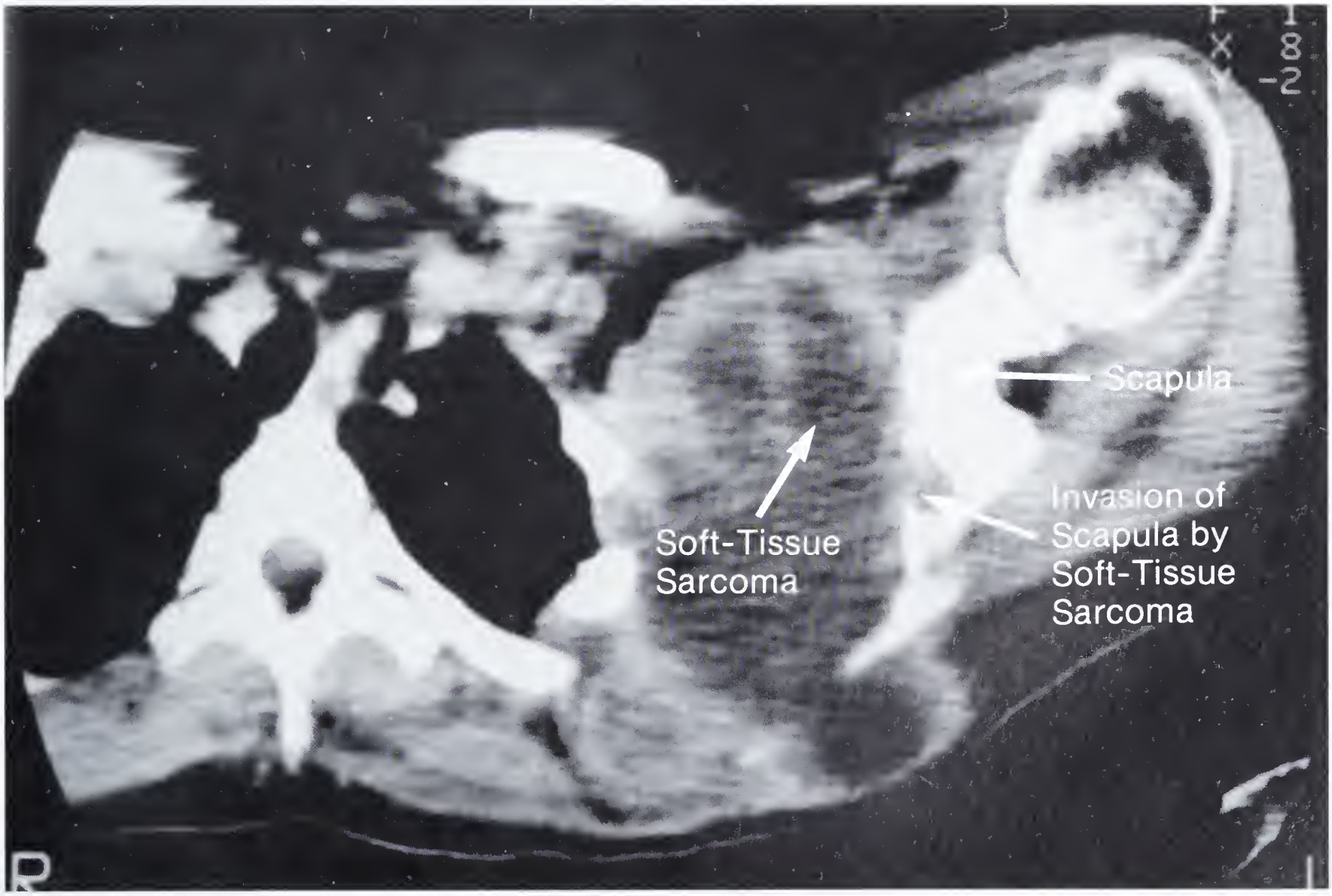

Figure 2: CT scan showing bone involvement of scapula.

Results

The results of bone scanning and CT are summarized in Table 2.

Table II
Determination of Bone Involvement by Bone Scan and Computed Tomography

Result of Scan	Operative and Pathology Findings			
	Bone Involved		Bone Uninvolved	
	bone scan	CT scan	bone scan	CT scan
Bone Involved	3	7	0	4
Bone Uninvolved	4	1	4	0
Indeterminate	2	1 missing	0	0

Bone Scanning

Bone scans were interpreted to show bone involvement in three patients who were confirmed to be positive for bone involvement anatomically. There were no false-positive scans. Bone scans were also interpreted to show bone to be uninvolved in eight patients. Four of these patients were anatomically proven true negatives. However, in the other four negatives, bone was found to be involved pathologically. Of these four false-negatives, two had direct invasion of the bone or periosteum by tumour, while two had microscopic invasion by tumour cells within five mm of bone without evidence of tumour cells invading into bone or periosteum.

Two bone scans were considered indeterminate for bone involvement and both were subsequently found anatomically to involve bone. In one case, there had been previous resection and subsequent high dose radiation to the area. Thus, it could not be determined whether changes seen on bone scan were due to bone involvement by tumour or bone reaction to previous radiotherapy. High dose radiation has been found by others to cause problems in the interpretation of bone scans.[10] The other patient had concomitant reflex sympathetic dystrophy (RSD), which causes a diffuse uptake of isotope. It was impossible to determine if the abnormal uptake in bone was caused by tumour infiltration or RSD.

Computed Tomography

Eleven of twelve CT scans reviewed were found to indicate bone involvement. Of these, seven were proven anatomically to involve bone. The other four patients were proven false positive for bone involvement. In one false positive scan, the image on CT was not optimal; this may have contributed to the incorrect result. In another patient, chronic lymphedema in the region of the tumour may have obscured the tumour margin, again contributing to a false result.

The only scan which did not show bone involvement was proven to be anatomically false-negative. This patient also had a false negative bone scan. In this case the tumour was found to be within a five mm margin of bone without direct invasion of bone or periosteum.

Table three summarizes this data, showing the accuracy, specificity, sensitivity, positive predictive value and negative predictive value for both techniques.

Table III
A Comparison of the Informative Values of CT and Bone Scanning

	Bone Scan (N=13)	CT Scan (N=12)
Accuracy (TP+TN/All Cases)	7/13 (54 %)	7/12 (58%)
Specificity (TN/TN+FP+Indet)	4/4 (100%)	0/4 (0 %)
Sensitivity (TP/TP+FN+Indet)	3/9 (33 %)	7/8 (88%)
Predictive Value (+) (TP/TP+FP)	3/3 (100%)	7/11 (64%)
Predictive Value (-) (TN/TN+FN)	4/8 (50 %)	0/1 (0 %)

Discussion

The definition of an "adequate" surgical resection has gradually changed over the past fifteen years. Enneking's concept of the radical resection (i.e., resection of the entire limb compartment from origin to insertion) has been replaced by the more conservative "wide" resection (i.e., removal of the tumour with a thin layer of normal covering tissue).[2,9,13,19] This is generally accompanied by adjuvant radiotherapy.

However, despite the success of radiotherapy in permitting the surgeon to remove less normal tissue with the tumour,[20-23] it has been shown that lesions resected with positive microscopic margins have an unacceptably high incidence of local relapse, even when radical radiotherapy is administered to the patient.[24] Since local reccurance is associated with a high risk of systemic relapse and patient mortality,[6,24-26] it is crucial that the surgical resection not leave microscopic tumour in the wound. Detailed information about the anatomical relationships of the lesion to vital structures within the extremity is therefore fundamental for an optimal procedure that maximizes both extremity function and oncological control.[9-13]

Evaluation of the tumour-bone interface is particularly important in planning the tumour resection. In a study of nineteen patients with "difficult" mesenchymal tumours, Bell and O'Sullivan demonstrated that resection of a lesion approximating the skeleton resulted in a late pathological fracture in three of three patients.[27] The partially resected long bone is generally within the high-dose radiation field, which inhibits the bone remodelling necessary for stress transference around an area of cortical resection. Avoidance of bone resection in soft tissue sarcoma is therefore important unless it is absolutely necessary to achieve negative margins. We feel that a preoperative finding of tumour within

five mm of the bone necessitates skeletal resection unless this margin can be improved by intra-operative positioning of the extremity or the lesion. In developing criteria for preoperative evaluation of imaging studies, we therefore defined five mm as the CT scan criteria for bone involvement.

CT in the past has provided the most accurate anatomical localization of STS.[5,8,9,12,14,16] However, delineation of tumour and adjacent structures on CT is best when tumour is surrounded by fat or has significantly different attenuation values than surrounding soft-tissue.[8,11,16] When the patient is thin,[10,11,16] when the lesion is in the distal extremities (because of their small size and lack of fat),[16] when perimarginal edema is present,[10,14] when pressure within the soft-tissue compartment obliterates the radiological plane between tumour and bone[9] or when the tumour itself has indistinct margins,[11] the exact relationship of the tumour to surrounding structures may be unclear.[9-11,14,16]

Thus, CT may not always accurately depict the spatial relationship between the sarcoma and adjacent bone.[10,11] Some researchers have shown bone scanning to be more useful than CT (or plain radiography) in the evaluation of bone involvement by adjacent tumour.[10,11,14] One prospective study of seventeen patients has shown bone scanning to have a sensitivity of 100% and a specificity of 86%. This compared favourably to CT with a sensitivity and specificity of 80% and 43% respectively in detecting bone involvement by tumour.

In this study, bone scanning was found to have a much lower sensitivity (33%) than CT (88%). However, bone scanning had a much higher specificity (100%) than did CT (0%). In fact, overall accuracy for both modalities was virtually equivalent, 54% for bone scanning compared to 58% for CT scanning.

There were four false-negative bone scans and one false-negative CT scan. In two cases where bone scanning was found to be false-negative, tumour did not invade bone directly but was found within five mm of bone. This may indicate that bone scanning is better able to detect direct bone invasion by tumour cells than tumour proximity to bone. However, this is not clinically relevant. As five mm is the resection margin necessary to permit dissection of the tumour without microscopic contamination of the resection margins with tumour cells, generally bone resection was necessary in these cases to prevent local relapse.[18,24]

Bone scanning had a higher positive predictive value (100%) than did CT (64%). Since the cases were selected by the clinical finding that the tumour approximated the skeletal structures, the patients selected for the study had a high prevalence of bone involvement by STS (9 of 13 patients or 69%). A high prevalence increases the probability that a positive result indicates disease, i.e., increases the positive predictive value of a test.[28] Despite this, the positive predictive value of CT scanning was only 64%, indicating that in this study a CT scan showing bone involvement did not provide reliable information. This result may be generalized to a typical population of STS patients with a much lower prevalence of bone involvement. False positive results would not be expected to increase significantly in this

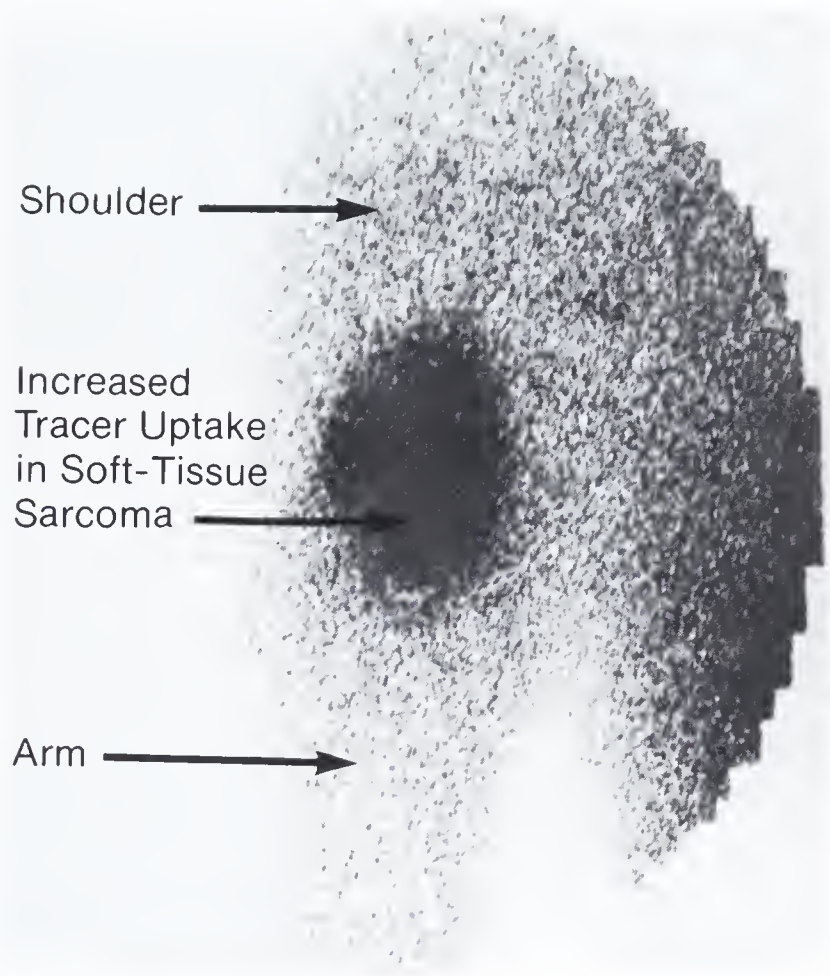

Figure 3: Bone scan showing bone involvement of humerus.

population as in many patients tumour would not approximate bone. However, with a much lower incidence of bone involvement, true positive results could not be expected to rise either. Thus, the positive predictive value for a typical population of STS patients would not be expected to deviate greatly from 64%. Therefore, in a typical population of soft-tissue sarcoma patients, a CT scan showing bone involvement may have very limited utility.

Although the sensitivity of CT scanning was found to be 84%, eleven of twelve patients with CT scans were found to be positive for bone involvement by this modality. Four of these patients were false-positive. The positive predictive value of CT scanning (64%) indicates that a positive result for bone involvement by CT scan has a 44% probability of being false-positive. Obviously, acting on the determination of bone involvement by CT scans alone would lead to unnecessary bone removal and loss of function. As all positive results in bone scanning were anatomically proven positive and were also positive on CT scans, a bone scan may be useful to confirm bone involvement shown on a CT scan. However, because of the low sensitivity found for bone scanning in this study, a negative bone scan can not rule out bone involvement. In two cases bone scanning was unable to determine bone involvement and in four cases the bone scan results were misleading. Thus, the usefulness of bone scanning in determining direct bone involvement by tumour can be questioned.

Accuracy for both modalities was poor, 54% for bone scans and 58% for CT scans. From this experience, it can be seen that a more accurate modality to determine bone involvement by adjacent STS is needed. MRI may emerge as this modality. To date, research indicates this may be the case.[14,29]

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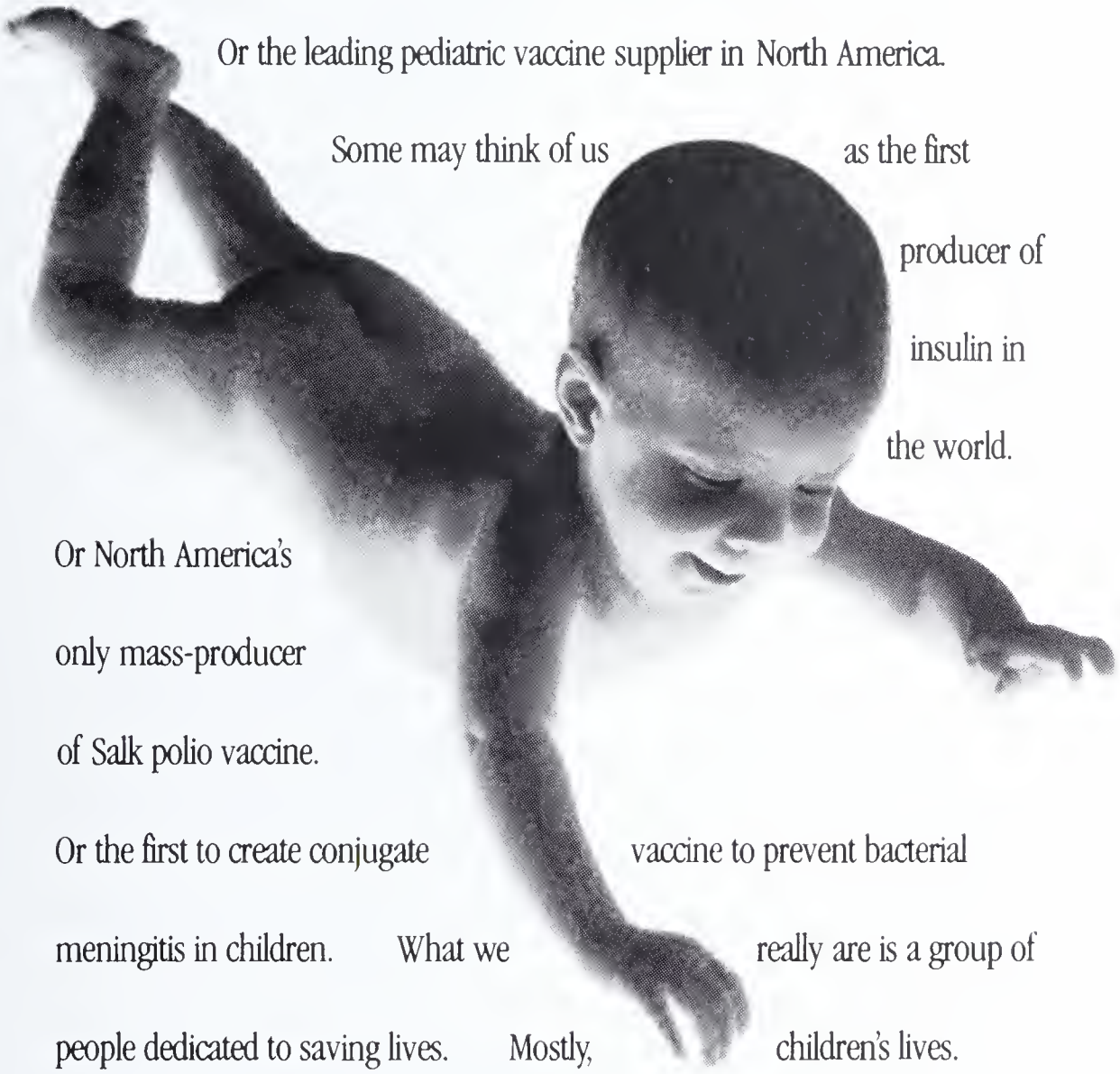

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A 56 Year-Old Woman with Severe Diffuse Abdominal Pain and Tenderness with Previous Episodes of Intermittent Crampy Right Lower Quadrant Pain

Michael J. Weinberg, M.Sc., 9T0
*Christopher Jamieson, M.B., B.S., F.R.C.S.C., F.A.C.S.**

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Case Report

A 56-year-old woman was admitted to hospital because of severe continuous abdominal pain of one day's duration.

The day before admission she had developed crampy right lower quadrant pain. The pain became severe, did not resolve, and although initially confined to the right lower quadrant now involved the entire lower abdomen. She also described nausea and vomiting and had had no urine output or bowel movements for one day.

Further questioning revealed a history of previous episodes of mild right lower quadrant intermittent crampy pain starting 4 years previously. The pain at that time had gradually radiated throughout the lower abdomen and through to her back, eventually becoming steady with accompanying nausea and vomiting and marked abdominal distention so that she could not do up her skirt. The pain relented gradually and spontaneously after about four days, leaving only slight residual tenderness. Up until the pain became severe she had been having normal daily bowel movements with no blood but for about four days at the height of her pain she passed no stool or gas. She subsequently had four more such attacks before her current admission. In the interval between, her abdomen was perfectly comfortable with no change in bowel habit.

Her past health had otherwise been good apart from a total abdominal hysterectomy and bilateral salpingo-oophorectomy in 1982 for a carcinoma of the uterus. She had been followed regularly with no evidence of recurrence. She had a brother who died of carcinoma of the colon three years previously. She denied any allergies and was still on malaria prophylaxis as she had recently returned from East Africa.

On physical examination she was a pale 56-year-old woman, looking anxious and distressed, lying supine and reluctant to move.

Her temperature was 37.5 degrees Celsius, heart rate 148, blood pressure 120/86 (right arm, supine) and her respiratory rate was 20 with respirations being very shallow. No cutaneous lesions were found. There was no lymphadenopathy. The head and neck were normal. The lungs were clear and there was a grade II/VI systolic murmur heard loudest at the lower left sternal border. The abdomen was very distended. There was a scar from a previous lower abdominal transverse incision. The patient when asked to cough complained of severe abdominal pain. There were no bowel sounds and there was diffuse abdominal tenderness and guarding on light palpation. There was no rebound tenderness evident. Rectal examination revealed fecal impaction, no pelvic abscess and no occult blood. Pelvic examination was unremarkable. All hernial orifices were normal. There were no abnormalities of the limbs and the genitalia were normal. A Foley catheter was inserted and drained 50 ml of concentrated urine. Microscopic examination of the urine was normal. The hemoglobin was 140 g/L, and the white cell count was 14.5x10(9) with 80% neutrophils and 10% band forms. The urea nitrogen was 11.8 mmol/L, the glucose 16.0 mmol/L, the sodium 130 mmol/L, the potassium 5.0 mmol/L, the chloride 102 mmol/L, the bicarbonate 8 mmol/L, the creatinine 177 μmol/L, and the serum amylase 96U/L. An electrocardiogram revealed a sinus tachycardia, with no ST segment or T-wave changes. An x-ray film of the chest disclosed normal heart, hilum and lung fields.

A diagnostic procedure was performed and a decision made as to the appropriate therapy.

Review of History

In assessing abdominal pain, one must first formulate some concept of the underlying process based on the history. It is usually possible to narrow down the possible diagnoses before embarking on the physical examination, and subsequently to make a provisional diagnosis which may require confimation with appropriate investigations.

The key features in the history are the nature of the pain and its location. This patient described severe crampy abdominal pain which later became continuous. Crampy pain would indicate smooth muscle spasm secondary to obstruction of a hollow viscus such as bowel, ureter, bile duct or gallbladder. The change to a continuous severe pain suggests ischemia or inflammation had developed in the organ affected. The location of the pain in the right lower quadrant is significant, and it is useful to think of the anatomy of the right

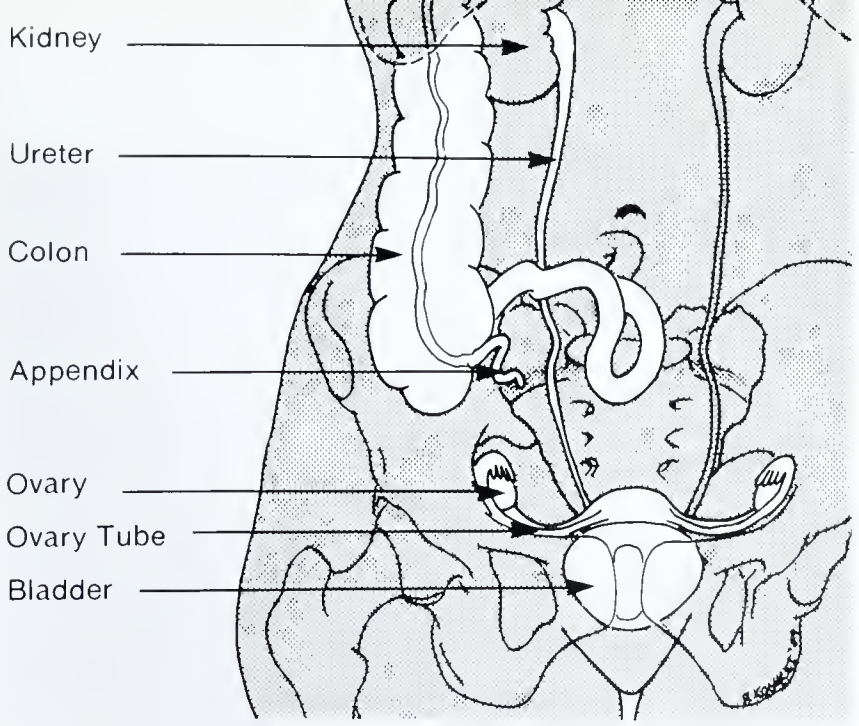

Figure 1: Anatomy of the RLQ. The location of the pain in the RLQ is significant and it is useful to think of the anatomy of the RLQ when considering possible diagnoses.

lower abdomen when considering possible diagnoses. (Fig. 1) This therefore makes the biliary tree an unlikely site, narrowing down the possibilities to bowel, ureter, or fallopian tube. The accompanying nausea and vomiting are also consistent with an obstruction of distal small bowel or colon. This is supported by her description of having passed no stool or gas for four days at the time of her pain.

Her previous history of intermittent right lower quadrant crampy abdominal pain would suggest a recurrent condition as the cause of her current problem. The pain had always resolved spontaneously with these episodes, but the slight residual tenderness that she had been left with on previous occasions would suggest that there had been some residual inflammation at the site.

Review of her previous health is useful and reveals that she had undergone total abdominal hysterectomy and bilateral salpingo-oophorectomy. One can therefore safely exclude a gynecological cause of her pain. The possibilities that would have otherwise been considered would have been a twisted or ruptured ovarian cyst, or in a younger woman an ectopic pregnancy or an infectious salpingitis. Adhesions causing bowel obstruction and occasionally strangulation must be considered in any patient who has previously undergone abdominal surgery.

Thus, based on the history, it would appear that this patient had suffered another episode of a recurring problem that involved obstruction of a hollow viscus in the right lower quadrant of the abdomen, and that on this occasion the problem had progressed to ischemia or obstruction of that organ. The constipation and vomiting would suggest the obstruction was intestinal (i.e., in the distal small bowel, appendix or right colon) rather than in the urinary system.

Review of Physical Findings

The significant features on physical examination were that she seemed anxious and distressed, was lying supine and was reluctant to move, had a tachycardia and shallow respirations. These are the classical systemic signs of peritonitis as first described by Hippocrates. The abdominal distention suggests obstruction although a paralytic ileus may also cause accumulation of intestinal gas. Abdominal examination confirmed the presence of peritonitis in that she complained of severe abdominal pain when she coughed or moved. There was diffuse abdominal tenderness and guarding, and bowel sounds were absent — the usual abdominal findings in peritonitis. (Fig. 2) In such a patient it is unnecessary and indeed cruel to attempt rebound tenderness, a test that is useful only if there is doubt about the significance of abdominal tenderness. An important observation was that all hernial orifices were normal

Figure 2: The classic features of peritonitis

Pelvic and rectal examinations are essential to the diagnosis of pelvic peritonitis

thus excluding a strangulated hernia as the cause of bowel obstruction and peritonitis.

The findings of peritonitis on physical examination with absent bowel sounds further confirmed that her underlying problem originated in bowel. Peritonitis complicating obstruction implies either perforation of the bowel, or (more likely) strangulation leading to ischemia and necrosis of small bowel. Perforation is a more common complication of distal large bowel obstruction and is not usually a complication of small bowel obstruction. The cecum, because of its larger diameter, is the commonest site of perforation associated with distal obstruction. Strangulation is more often seen in the more mobile small bowel rather than the large bowel which is tethered by its peritoneal attachments. However both the cecum and the sigmoid colon can twist on the mesentery as a volvulus which may lead to ischemia and subsequent infarction.

Thus, the differential diagnosis at this point should include strangulated and/or infarcted small bowel, appendicitis, volvulus of the cecum, or a perforation of the cecum caused by a distal colon obstruction.

Review of Investigations

The initial steps in the emergency department should be the resuscitation of the patient and the conduct of any necessary investigations to confirm the diagnosis so that a decision regarding management can be made.

The clinical diagnosis of peritonitis is an absolute indication for a laparotomy. Although this patient is not hypotensive the usual progression in such a case would be for septic shock to develop if the underlying problem is not corrected. Thus immediate resuscitation with fluid and electrolyte infusion is required before the patient is taken to the operating room. A Foley catheter is useful in that it permits continuous observation of urine output, so that the adequacy of fluid resuscitation can be monitored.

A chest X-ray should be obtained in any patient with any acute abdominal condition, if only to exclude an associated pneumonia. Plain x-rays of the abdomen are not necessary if the decision has already been made to proceed with laparotomy based on the clinical findings. However, if there is any doubt, plain X-rays taken in three views may demonstrate dilated loops of bowel with air fluid levels, confirming the clinical diagnosis of obstruction. A closed loop obstruction, for example from a volvulus of bowel, would be seen as a very large dilated single loop of bowel. Free intraperitoneal air is usually seen in a patient with a bowel perfortion, although this free air is best seen beneath the diaphragms on the upright chest X-ray.

Other routine investigations of such a patient in the emergency department should include a CBC to exclude the possibility of anemia, and it is likely that in this patient there would be a leukocytosis confirming an inflammatory process in the abdomen. Electrolytes should be done routinely, especially as the patient had been vomiting and abnormalities of the serum potassium and chloride are quite likely. The bicarbonate in this patient was low which is consistent with a metabolic acidosis. A metabolic acidosis in a patient with a acute abdominal condition would suggest ischemia or infarction of bowel. The serum creatinine is routinely measured with the serum electrolytes and is useful because of the possibility of renal impairment secondary to the fluid depletion that the patient had suffered. A serum amylase estimation should be done routinely in a patient with acute abdominal pain as acute pancreatitis, which may cause severe peritonitis and shock, will almost always be associated with an elevated serum amylase.

Microscopic examination of the urine of a patient with acute abdominal pain in the emergency department should be routine. A ureteric stone, which should be considered in the differential diagnosis of right lower quadrant pain, would usually be associated with gross or microscopic hematuria. A ureteric calculus may cause right lower quadrant pain, occasionally with associated localized tenderness. A urinary tract infection, possibly with pyelonephritis, may mimic an acute intra-peritoneal process and may even be associated with nausea, vomiting, and abdominal distention. Costovertebral angle tenderness would usually be present.

A gynecologic cause must be considered in any woman with acute right lower quadrant abdominal pain. Assessment in the emergency department must therefore include a pelvic examination, and ultrasound of the pelvis can usually be obtained at short notice. This patient, however, had previously undergone hysterectomy and bilateral salpingo-oophorectomy.

Having excluded a gynecological or urinary tract cause of this woman's right-sided abdominal pain, the most likely diagnosis can be narrowed down to an inflammatory process of bowel associated with obstruction.

Differential Diagnosis

Acute appendicitis is a clinical diagnosis based on the history and the finding of localized right lower quadrant peritonitis. Obstruction, which was a feature in this case, would be unusual with appendicitis, although the initial central abdominal colic often experienced with appendicitis may be indistinguishable from small bowel colic. Recurrent abdominal pain over a period of 4 years is unlikely to be from appendicitis.

Diverticulitis is a common cause of acute abdominal pain in the elderly. It most commonly affects the sigmoid colon and thus usually presents with left sided lower abdominal pain and tenderness (and occasionally a mass), but it may occasionally present with right sided symptoms and signs.

Obstruction of the small intestine causes cramping periumbilical, central abdominal pain. Vomiting usually follows the onset of pain after an interval that varies with the level of obstruction. The more proximal the obstruction the more profuse the vomiting. The physical findings are minimal tenderness with loud, frequent and high pitched bowel sounds. Abdominal distention is a feature of more distal bowel obstruction. The diagnosis is confirmed with plain abdominal X-rays which show dilated small bowel loops with air fluid levels. The key decision in the management of a patient with small bowel obstruction is whether or not there is ischemia or

A

B

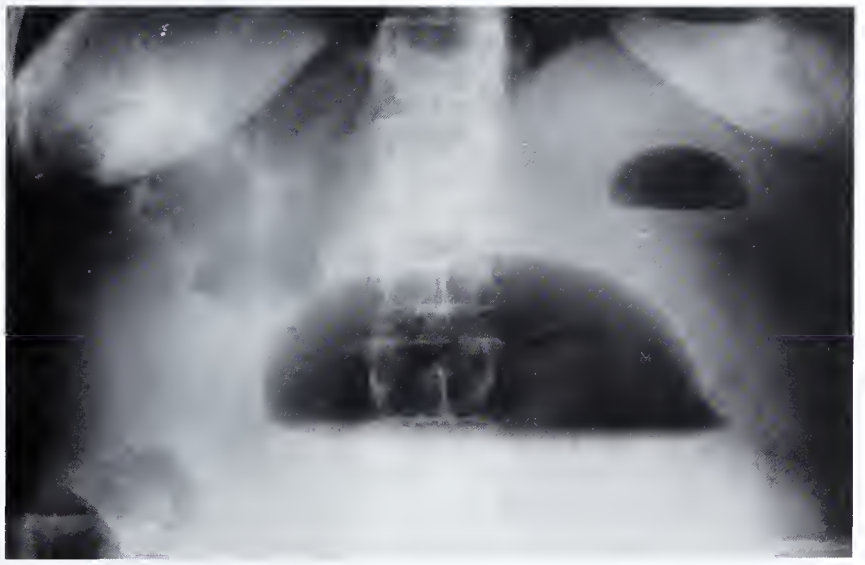

Figure 3: Plain abdominal X-rays taken in the emergency department – (a) supine and (b) upright areas.

infarction present. Strangulation would be suggested by the presence of severe continuous pain, abdominal tenderness and especially signs of peritonitis, with decreased bowel sounds and systemic signs of toxicity such as a fever or tachycardia, leukocytosis, and a metabolic acidosis.

Large bowel obstruction, most commonly caused by a carcinoma in the left colon, is associated with an inability to pass flatus or feces, abdominal distention, lower abdominal cramps, with the features on the abdominal examination being abdominal distention and high pitched bowel sounds. Strangulation of large bowel does not occur unless there has been volvulus of the mobile portions of the colon i.e., the sigmoid and the right colon. Untreated large bowel obstruction may eventually lead to a cecal perforation, especially if the ileocecal valve is competent.

Management of Patient

The diagnostic procedure performed was plain radiography of the abdomen. X-rays (3 views) of the patient in the emergency department showed a massively dilated loop of bowel thought to be cecum (Figure 2). The diagnosis of a cecal volvulus was made. Following resuscitation the patient was taken to the operating room where a massive cecal volvulus with infarction was found. The cecum and right colon was resected and a primary anastomosis was performed between terminal ileum and transverse colon. The patient made an uncomplicated recovery.

Although volvulus of the cecum is less common than volvulus of the sigmoid colon, the mechanism is identical. The bowel twists about a narrowly based mesentery forming a closed loop of obstruction. The twisting usually causes venous occlusion initially, with subsequent engorgement of the mesentery causing arterial occlusion leading to gangrene and subsequently perforation. The twisting of the bowel causes complete occlusion of the lumen. The diagnosis is usually apparent on plain X-rays of the abdomen, but if any doubt remains a barium enema will confirm the diagnosis and show a classic "bird's beak" occlusion of the colon.

Transient volvulus of the colon may resolve spontaneously with detorsion and resolution of the obstruction. This is what in fact had happened to this patient on 4 previous occasions. A barium enema had been done at that time and had shown a very mobile or 'floppy' cecum. Often, surgical correction is necessary and detorsion of the cecal volvulus at laparotomy may be possible without resection being necessary. However, a more definitive procedure is desirable to prevent recurrent volvulus and techniques used have included suturing of the cecum to the abdominal wall, or the creation of a temporary cecostomy to create fixation of the cecum to the abdominal wall. Many surgeons now feel that resection is the most effective treatment and resection with primary anastomosis can be safely performed in most patients. In the absence of gross peritoneal contamination from a perforation an anastomosis following resection would be preferable to an ileostomy.

In summary, the presenting features of this patient are typical of a cecal volvulus leading to strangulation and infarction. Initial symptoms of crampy abdominal pain together with nausea and vomiting are consistent with bowel obstruction. The severe persistent pain associated with diffuse tenderness occurred because of infarction of the cecal volvulus and ensuing peritonitis. Although this condition is not common, the approach used in this case can be applied to most acute abdominal conditions.

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Wound Suturing - "How Do I Do It?"

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Abstract

The ability to perform precise atraumatic suturing is an essential skill to acquire. Suturing, although almost an art form, requires a knowledge of the basic principles of wound healing as well as actual technical experience. The techniques and principles of wound suturing are neglected in our curriculum and later there is also a lack of supervised practice. However, we can expect to be frequently called upon to suture wounds in an expert fashion. This article will briefly review the essential techniques and basic principles of wound suturing which are useful for all students, especially those during the often "intimidating" surgery rotation.

Introduction

The goals of wound care in the primary care setting are to stop bleeding, prevent infection, speed healing and preserve the appearance and function of the injured area.[1] Suturing is often an important part of this. Incorrect wound closure can lead to dehiscence, seromas, hematomas, infection and poor cosmesis.[1]

A review of basic anatomy of the skin is important. Although single layer closure (skin alone) is sometimes done, it is more common to perform a multilayered closure. The skin and underlying tissues are composed of five basic layers. These are from superficial to deep: the epidermis, the dermis, the subcutaneous tissue and superficial fascia, the deep fascia, and the underlying tissues (usually muscle and bone). The model used in this article is presented in Figure 1.

Figure 1: Basic anatomy of the skin and the underlying tissues.

Sutures placed in fat and muscle are weak as opposed to fascia and dermis which give excellent support if they remain in place while the wound grows in tensile strength. The strongest component of the skin is the dermis.[2] Fascia repair also provides significant strength.

Wound Healing

Healing by primary intention implies there is physical approximation of the wound edges.[2] The initial phase is the inflammatory phase and occurs during the first week. In it the biochemical and cellular components for healing accumulate. During the second and third week fibroblasts proliferate and begin collagen synthesis. This is the proliferative phase. As the collagen content rises, wound strength increases, and within 7-14 days, the wound will generally have enough strength so that all sutures can be removed.[4] The scar will look the worst 3-5 weeks after closure, secondary to increased capillary and fibroblastic proliferation.[5,6,7] It is important to explain to the patient that it will take months for the process of remodelling to occur, resulting in the anticipated flat, fine line scar.

Healing by secondary intention implies healing of a gross physical gap between the wound edges, as occurs with an unrepaired laceration.[3] These wounds are prone to bacterial contamination and increased scar tissue production. Wound contraction by myofibroblasts plays an important part in wound healing by secondary intention.[8]

Presentation

History: A brief history of the injury is very important. Time since injury and the technique of initial wound care should be sought. A good general rule is that the infection rate rises after 12 hours, and few physicians would close any wound after 24 hours.[2] The mechanism of injury is important since it will indicate the amount of contamination and additional soft-tissue

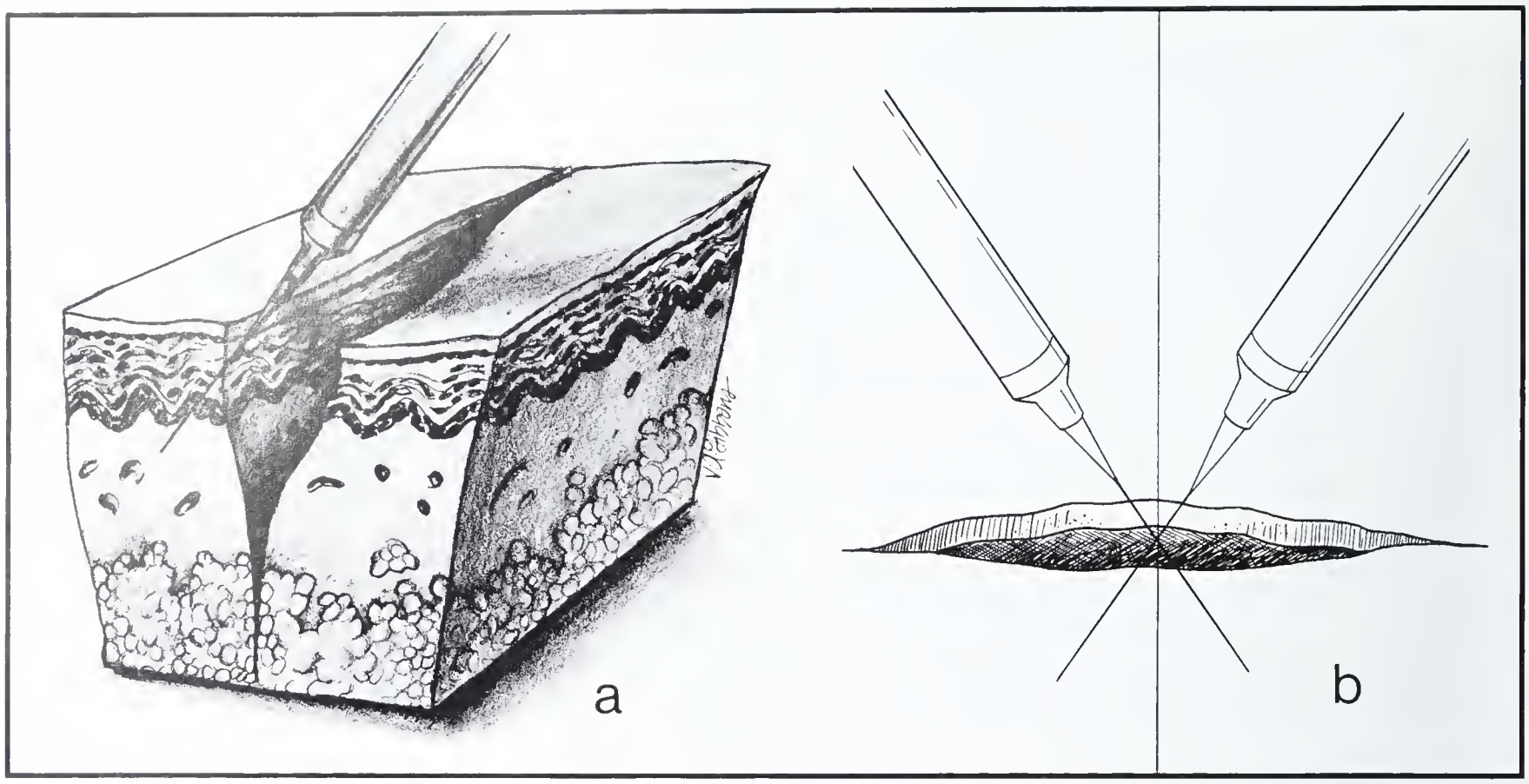

Figure 2: Local anaesthetic should be injected through the open edge of the wound(a) in a fan-like pattern through a single puncture site(b).

injury.[2] Active arterial bleeding and distal numbness suggest significant deep structure, i.e., vessel or nerve, injury. This can be confirmed by physical examination. Repair in this situation may have to be done in the operating room. Never forget to enquire about tetanus immunization. For prognostic reasons, note any history of keloid formation. Inquire about the presence of other diseases, such as diabetes mellitus, jaundice, uremia, cancer or chronic infection, since wound healing may be impaired.[3] Finally, always ask about allergies i.e., local anaesthetics or medications.

Examination: Assess any peripheral signs of damage to neurologic or vascular structures, and determine the involvement of adjacent and underlying tissues.[1] When the wound is near a joint or tendon, put the limb through a complete range of active and passive motion and look for any occult injury.[9] It is also very important to locate any foreign bodies in the wound. Glass may be difficult to see with the naked eye but is generally visible on X-ray. Clinical examination of the wound is extremely important.

Anaesthesia

The wound should be anaesthetized before it is cleaned, as there is no point in subjecting the patient to unnecessary discomfort.[10] One percent lidocaine HCl (Xylocaine HCl, et al) is most commonly used in a 1:100,000 solution with epinephrine. The maximum dose is about 4-5 ml/kg (± epinephrine). Epinephrine should not be used in the fingers and toes. The solution should be injected into the open portion of the wound in a fan-like pattern, through a single puncture, as is shown in Figure 2.[10] The anaesthetic should be injected subcutaneously, not intradermally and a 26 guage, 3cm needle is recommended.

Preparation of the Wound for Closure

There are four basic steps in preparing the wound for closure. First, a surface cleaning with very mild detergent should be performed to remove all dirt. Second, a noncaustic antiseptic solution, such as poviodone-iodine (Betadine et al.), should also be painted on the surrounding skin surface.[2,9] Third, the wound should be extensively irrigated with balanced saline solution, preferably through some type of jet stream such as a syringe.[1] Finally, the wound should be draped with sterile towels and sterile technique used from then on. If the wound is dirty, it should be washed out with poviodone-iodine and then irrigated with saline to flush out the antiseptic.

The next step is debridement, which is the process of removing devitalised tissue and foreign matter. This converts the ragged laceration that may be dirty or contaminated into a clean surgical wound.[1] It is important to be meticulous since one wants to remove all damaged tissue but not create an unnecessarily large defect whose repair would be more difficult. There are several techniques for performing debridement. A recommended method is to carry the initial incision through the dermis with a scalpel and then complete the rest of the debridement with fine, sharp scissors.[11] Debridement with scissors alone is not recommended since the skin edges tend to be crushed and often irregular. Fragments of dirt should be removed with fine forceps.

Suture Materials

The ideal suture material should have several characteristics.[12] Firstly, it should persist and maintain strength until the wound is healed. Secondly, it should disappear from tissue once the wound is healed without

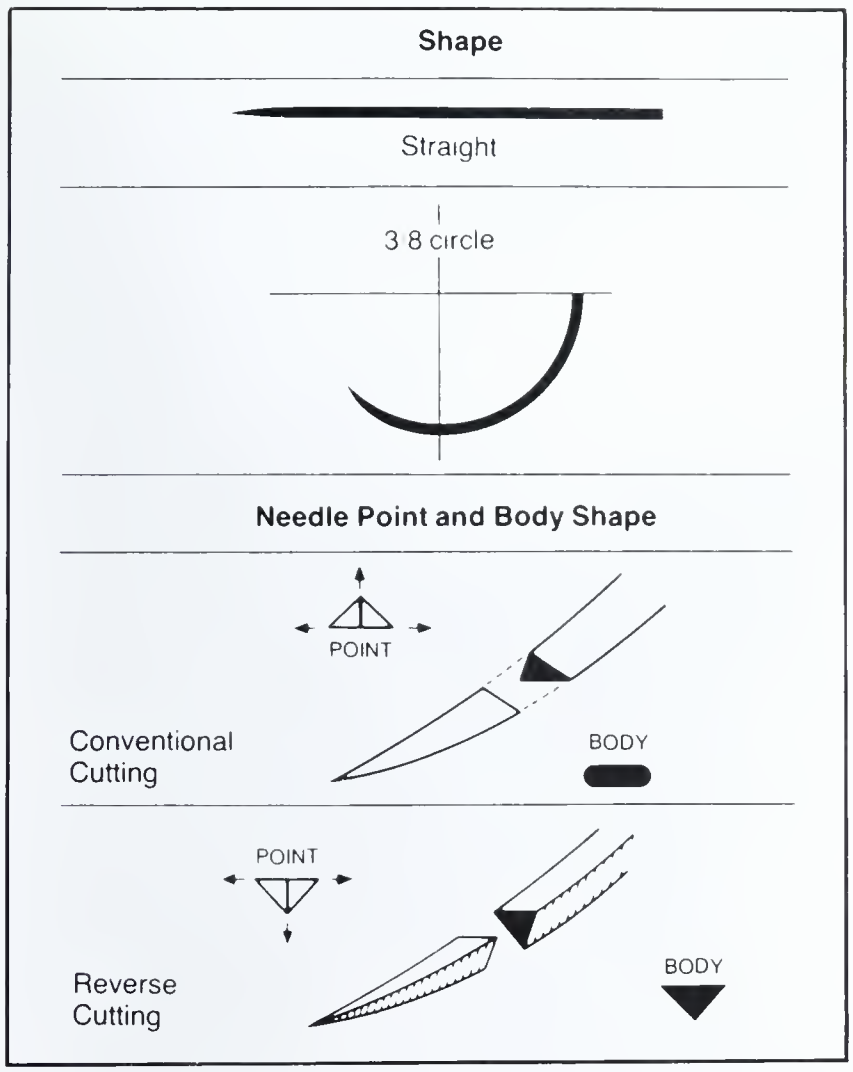

Figure 3: Common needle shapes and points. We recommend a 3/8 circle, conventional cutting, swaged needle.

scarring, infection or tissue reaction. Thirdly, it should hold a knot reliably and finally it should be easy to handle.

There are many types of suture materials. It is convenient to classify them as absorbable and non-absorbable. These can be further classified into either synthetic or biological. The synthetic sutures are further subdivided into monofilament or braided types. The following are the most commonly chosen.[12,13]

Absorbable sutures are used for subcutaneous closure. Different materials loose their tensile strengths at different times. Plain catgut (from sheep intestine), is used rarely since it absorbs quickly and causes a marked tissue reaction. Chromic catgut (catgut treated with chromium salts) lasts longer and incites less reaction. It is useful for ligating subcutaneous bleeders, and for closing the deep fascia. Dexon and Vicryl are synthetic absorbable sutures. These have a high tensile strength, hold knots very well and provoke minimal tissue reaction. However, since they are braided there is increased bacterial adherence and thus a greater risk of infection. They should be used sparingly in contaminated wounds. They are useful for subcuticular closure of wounds as well as repair of fascial layers.

Nonabsorbable, silk is still widely used since it handles and ties well. However, it provokes a moderate tissue reaction and thrombogenesis if used in vessels. Its braided structure is associated with an increased risk of infection in the skin. Silk is often an excellent choice in the scalp. Monofilament nylon and polypropylene create the least tissue reaction. They have a high tensile strength and since bacterial adherence is low so is the risk of infection. Since they are rather stiff, they handle less well and are difficult to knot. Knots can unravel spontaneously, therefore, one should tie at least four knots, one of which should be a surgeon's knot.[1] Nylon is probably the best and the most commonly used suture in cutaneous surgery. The choice of suture size is a matter of personal preference, but in general the smaller the better; 6-0 on the face, 5-0 on the arm and 4-0 on the leg and back are recommended.

Suture Needles

There are over 100 suture needles available.[12] They can be basically classified according to their shape (straight or curved), their points (cutting or non-cutting) and the method of suture attachment (eyes or swaged). Cutting needles can be further subdivided into conventional and reverse (Figure 3). There are some important features to note.[12] Curved rather than straight needles cause less tissue damage by following their own tract and everting tissue edges well. A partial circle, i.e. 3/8 is the best curve for a needle because the radius of the path is equal at all points of the needle path. The reverse cutting needle is less likely to cut tissue in its path and is stronger than the conventional cutting needle. Swaged needles are better than eyed needles in that they make smaller tracts and drag less

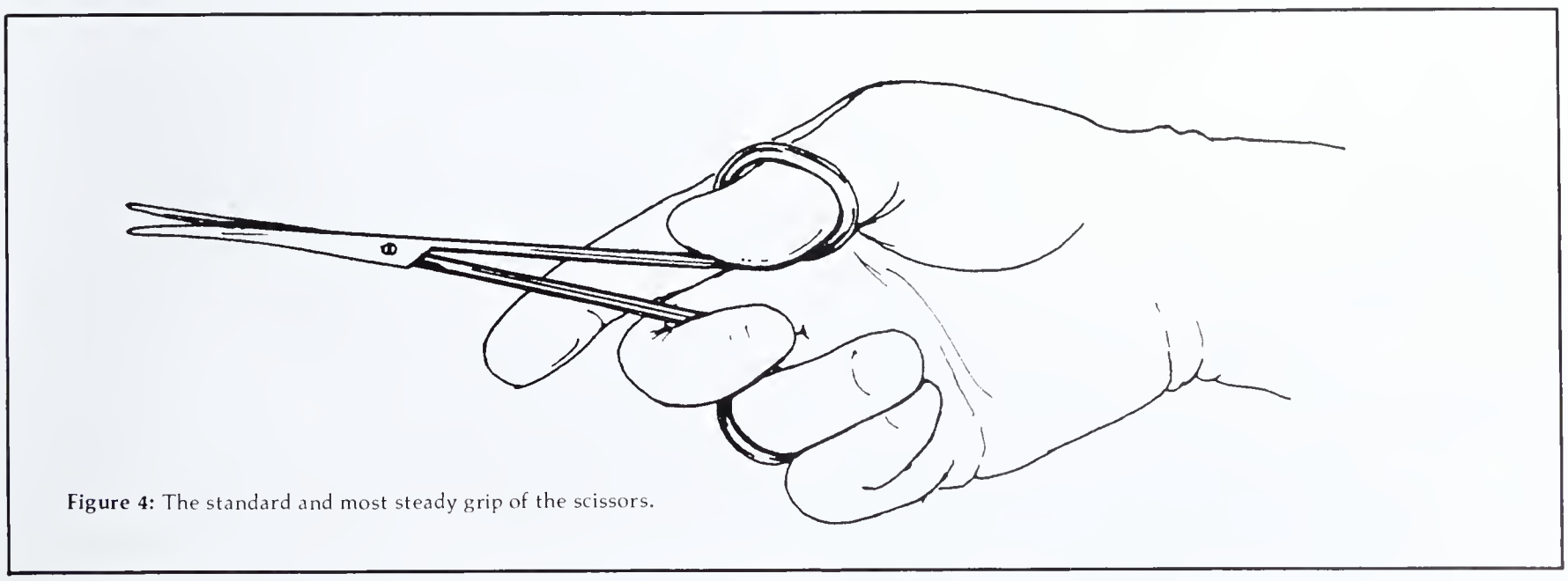

Figure 4: The standard and most steady grip of the scissors.

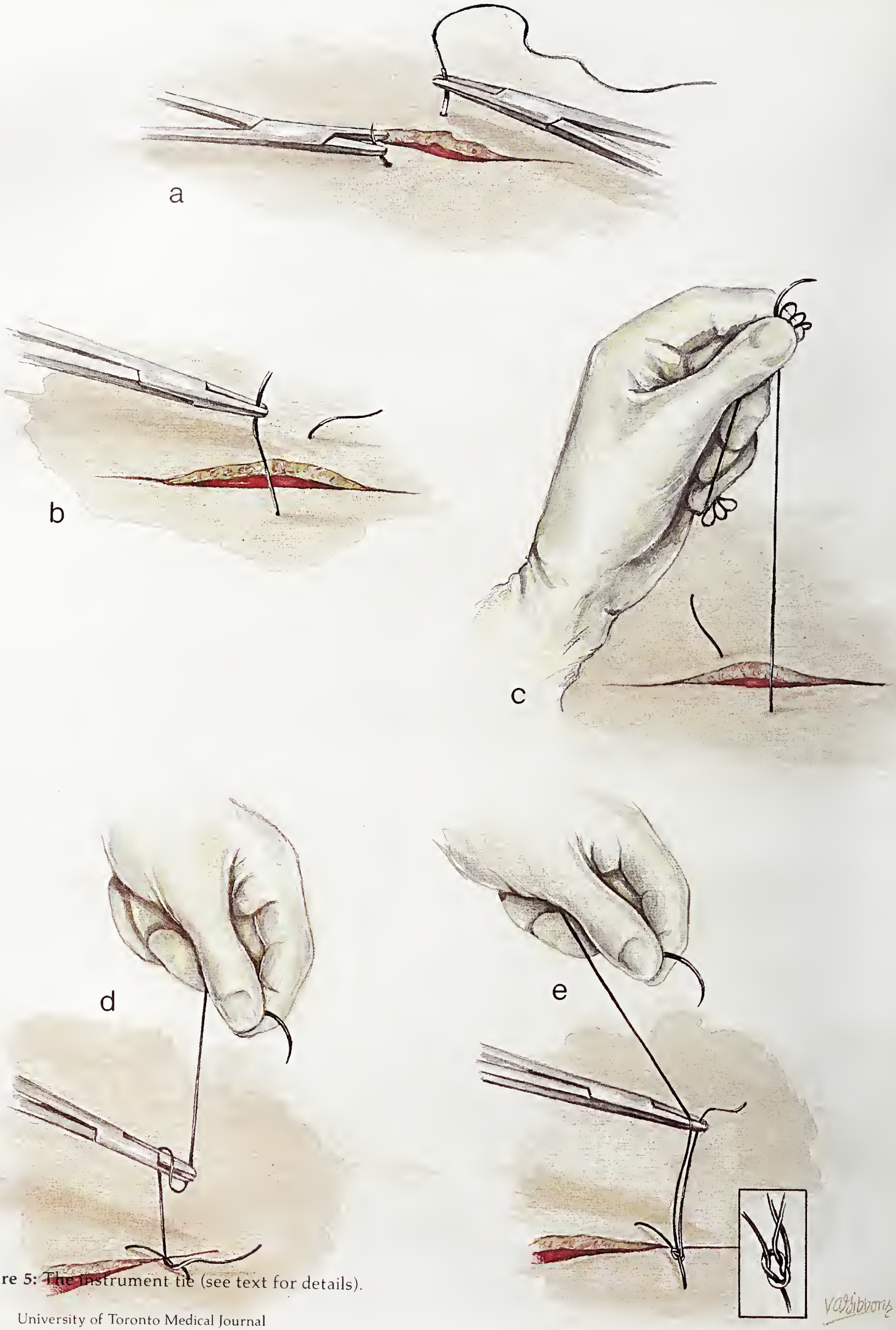

Figure 5: The instrument tie (see text for details).

suture material through tissue. Cutting needles are needed for skin and scar tissue. Non-cutting needles are used for tissues which have less resistance (i.e. blood vessels). These needles dissect through, rather than pierce tissue. Thus, we recommend a 3/8 circle, conventional cutting, swaged needle for the simple laceration.

Techniques of Wound Closure

The discussion will now turn to the various techniques utilized in wound repair. Surgical scissors vary in only 3 major design features: (a) tips may be sharp or blunt; (b) blades may be curved or straight; and (c) handles may be long or short.[14] The typical pair of 15 cm long scissors is designed and balanced for the normally sized adult human hand. Straight-bladed scissors with either long or medium length handles are ideal for cutting the ends of sutures. The standard and most useful grip is shown in Figure 4.[14] Three points of fixation against the hand allow for solid control. The thumb and ring fingers of the right hand are placed through the two finger rings of the scissors while the distal joints of the index and long fingers are curled beneath the shank. The index and long fingers thus provide stability and control the direction of thrust of the scissor tips. Remember the tips of the scissors are the business end!

Knots can be tied by hand or with an instrument. The instrument tie is advantageous since it speeds closure and conserves suture material. The needle holder allows one to precisely pierce the skin at the desired point and angle (90°) as shown in Figure 5(a). The needle tip is then grasped and withdrawn from the skin (figure 5a & b), following the curve of the needle. The suture material is drawn through the tissue until only a 2-4 cm short end remains. A knot is tied by taking a loop of the long end of the suture and throwing it over the tip of the needle holder (Figure 5d), the remaining short end is grasped, pulled down, and the knot is laid flat and tightened (Figure 5d). When the knot tension and skin edge approximation are ideal, the knot is squared by throwing a second loop in the suture material (Figure 5e) over the tip of the needle holder. This loop is flipped in the opposite direction from the first so that the knot will be squared. After several knots have been added, the short end of the suture is held up with the needle holder alongside the long end in the nondominant hand, and the suture is cut (Figure 5e).

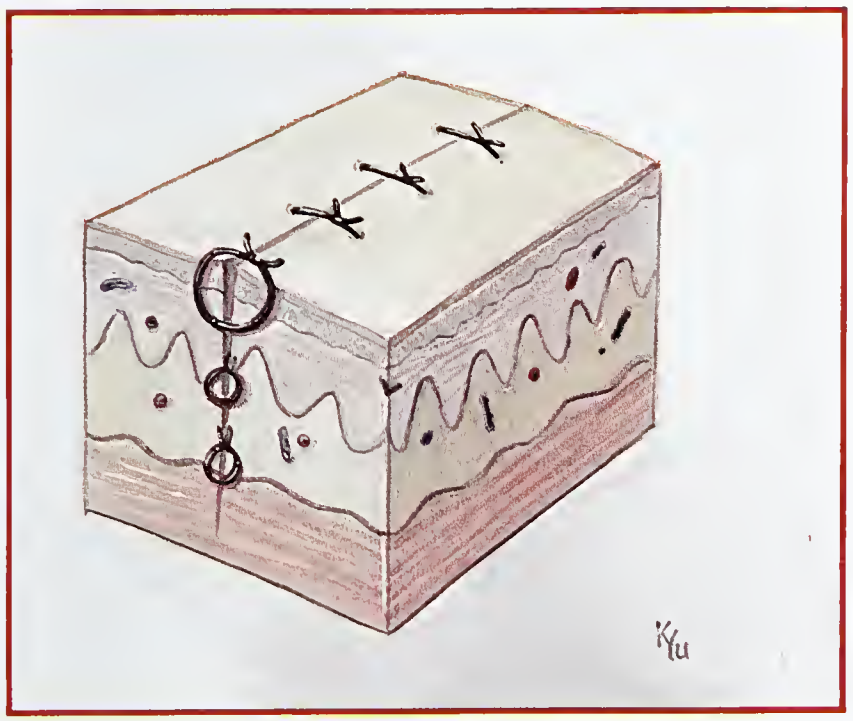

Figure 6: Layered closure should be used for most lacerations. Deep sutures reduce the ultimate tension on the epidermal sutures.

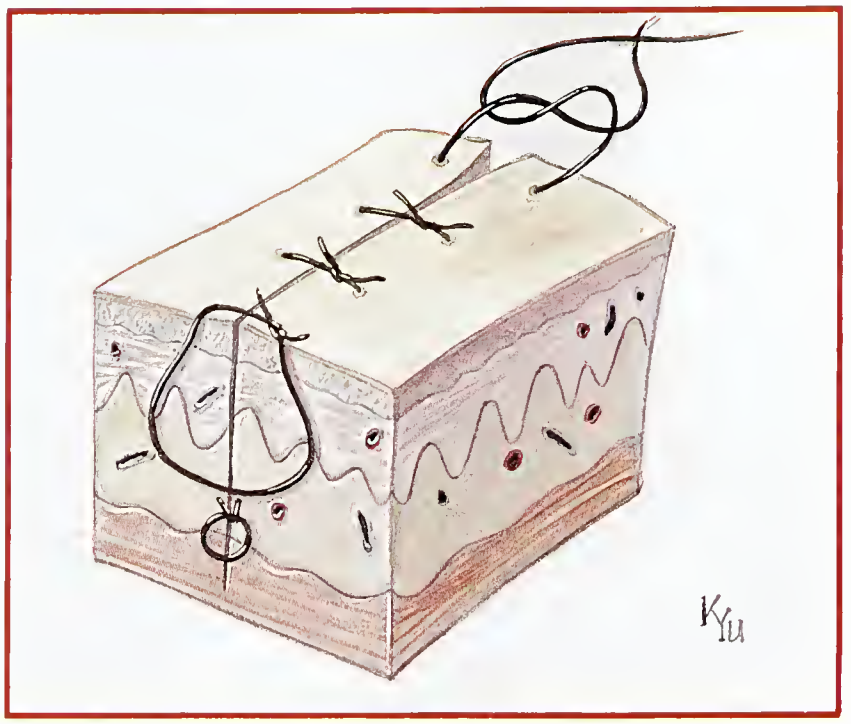

Figure 7: The Simple interrupted overlying loop stitch. The initial slightly raised wound will recede into the surrounding surface during the remodelling phase of healing. Note: all layers meet at the same level.

Basic Suturing Techniques

There are certain basic principles that must be adhered to in order to achieve optimal results. Some of these have already been discussed, i.e. use of the finest needle and the finest suture that will do the job.[12] Furthermore, one must be gentle with tissues, and a non-toothed forceps or a skin hook may be helpful in minimizing tissue trauma.

Perhaps the two most important principles are accurate approximation of the tissue layers and closure of all dead space.[1] Thus all tissue layers should meet at the same level. This mandates the use of a layered closure (Figure 6). Epidermal sutures should serve only to ensure proper opposition of skin edges.[1] The deep tissue layers that will retain sutures are the fat-fascia junction and the dermis, (Figure 5).[1] Deep sutures serve several functions. First they should align deep tissue layers. Second, they should obliterate dead space, and third they should reduce the tension placed on the skin closure (Figure 6). Thus the majority of tension should be borne by the deep sutures and an absorbable suture should be used. If the wound is closed so that the skin planes are approximated accurately, there is a good chance of obtaining an excellent scar. Another important principle is that of wound edge eversion. Sutures should slightly evert the wound edges. This creates a slightly raised wound which will recede into the surrounding surface during the remodelling phase of healing.[5] The simplest way to obtain eversion is by a simple interrupted everting loop stitch (Figure 7). The wound margin is entered from the epidermal side at a right angle. The needle is then angled so that the base of the

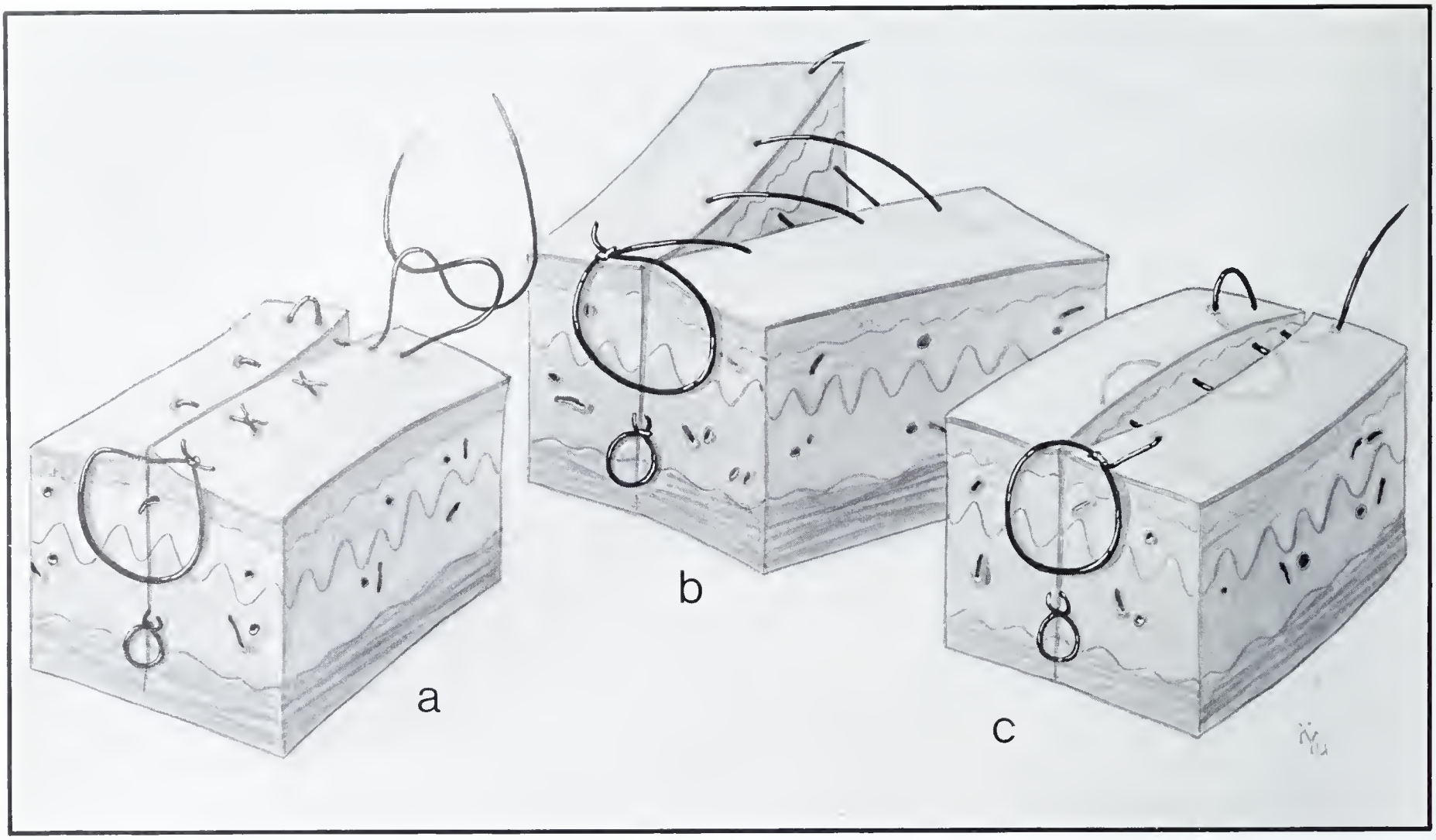

Figure 8: Various types of sutures. Vertical mattress sutures are shown in(a). The running cuticular sticth(b) is still popular and the continuous intradermal pull-out suture(c) is widely used.

suture is wider than the top. This ensures that the deeper layers bear the greatest tension. The needle is then brought through the wound. An equal amount of tissue is taken from the other side of the wound, and the distance from the wound edges should be equal on both sides. Finally the knot should be tied on one side of the wound. Swelling and inflammation increase a suture's tension, so that if the suture is placed too tightly it will tear the surface.[9] Moreover, when tension slackens as swelling recedes or the wound heals, the tear will leave a classic hatch scar.[9] Finally, sutures are placed as close together as necessary to obtain complete wound closure. In general, stitches should be placed as far back from the edge of the laceration as the skin is thick, generally about 3-5 mm.[10]

The vertical mattress stitch is another stitch for everting wound edges and can often be used in areas of thin skin or in areas of increased tension (ie. abdominal or chest incisions). Figure 8a shows the usual method of placement of vertical mattress sutures. Only as many of these should be used as necessary because interrupted simple cuticular sutures or a running intradermal pull out suture will generally give a superior closure.[14]

A popular stitch among many surgeons is the running cuticular stitch which is shown in Figure 8(b). This stitch is advantageous since it is easy and rapid, it requires minimal technical skill and the suture is readily removed postoperatively. On the negative side, it does not approximate skin as accurately as do either interrupted or properly placed intradermal sutures. It also tends to cause ischemia of the skin margins.

Another common stitch used by surgeons is the continuous intracuticular stitch (Figure 8c). The advantage of this stitch is that it eliminates stitch marks. This stitch should be placed through the superficial portion of the dermis. It is important to take equal bites at equal distance and to make sure the suture "glides" if it is to be removed. If it is completely buried, absorbable material can be used. The disadvantage of this suture is that it is not as strong as the interrupted suture.

Finally, after closing the laceration, one last inspection should be performed to ensure that the wound edges are approximated accurately. Some fine adjustments can usually be made with the forceps or skin hook at this time.[1] The wound edges should be cleaned gently with peroxide to remove all the antimicrobial agents and blood.[2] Remember, a clean wound usually means a happier patient. Some surgeons use Steri-strips to reinforce and seal the wound closure.[9] Most surgeons recommend a dressing to protect the wound and splint the repair.[15] Sutures should, in general, be removed as early as possible. It should be remembered that the skin sutures should not be primarily responsible for wound strength. If adequate deep closure has been performed, their early removal should be possible. Most authors agree that facial sutures should be removed within 5 days, (rich blood supply) and that all other sutures should be removed within 7 to 10 days, mainly due to the extra tension.[6,10,15] After suture removal, the wound can be reinforced with Steri-strips for several days.

Acknowledgements

The authors would like to thank Miss B. Eastaway for her expert help in preparing this manuscript.

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SYNTEX

The Retinoblastoma Gene and Tumour Suppression

David B. Mount, B.Sc., 9T0

Abstract

Genetic damage in cancer cells can result in the activation of "proto-oncogenes" and/or the inactivation of "tumour suppressor" genes. The retinoblastoma gene (RB) is the first tumour suppressor gene to be cloned and characterized. Recessive inactivation of RB is associated with the development of retinoblastoma and osteosarcoma, and may also have a role in the genesis of breast cancer and small cell lung cancer. Inactivation of other tumour suppressor genes appears to occur in several malignancies; future characterization of these genes will contribute considerably to the understanding of tumour initiation and progression.

Introduction

During the past decade, there has been substantial progress in the identification of genes which are involved in the development of cancer. Most research has centred on the oncogenes, a group of genes originally identified in human tumour DNA and in the genomes of oncogenic retroviruses.[1] Oncogenes arise from the somatic mutation of "proto-oncogenes", cellular genes involved in the control of normal proliferation and development. Somatic activation of a proto-oncogene can occur by point mutation, partial deletion, amplification or chromosomal translocation. All such mutational events result in expression of an active protein product, which must be present for neoplastic transformation to occur.[1]

Oncogenes have been said to be genetically dominant, in that an oncogene can transform a cell in the presence of its normal proto-oncogene counterpart.[1] In contrast, another class of genes has been identified for which the recessive loss of function induces cancer.[2-4] The loss of both alleles of such a gene leads to cancer, and the presence of one normal allele is thought to be sufficient to suppress tumour development. Accordingly, this class of cancer genes has been referred to as "tumour suppressor genes", "recessive cancer genes" or "anti-oncogenes".

There is considerable experimental evidence for the existence of genes which suppress tumour forma-tion.[2,5,6] In addition, the presence of such genes has been inferred from the study of certain childhood tum-ours and auto-somal dominant cancer syndromes.[4,7,8] The concept of recessive oncogenesis first arose from the genetic analysis of retinoblastoma, a rare childhood eye tumour with both hereditary and sporadic forms.[3] A gene with the proper-ties expected of the retinoblastoma gene has recently been cloned. This gene is inactivated in several other solid tumours, includ-ing osteosarcoma, breast carcinoma and small cell carcinoma of lung. Moreover, it appears that somatic inactivation of putative tumour suppressor genes may be a common event in the development of many sporadic and hereditary tumours.

An eight month-old child with unilateral retinoblastoma, presenting with leukocoria (white pupil) in the right eye. (picture courtesy of Dr. Brenda Gallie, Hospital for Sick Children, Toronto).

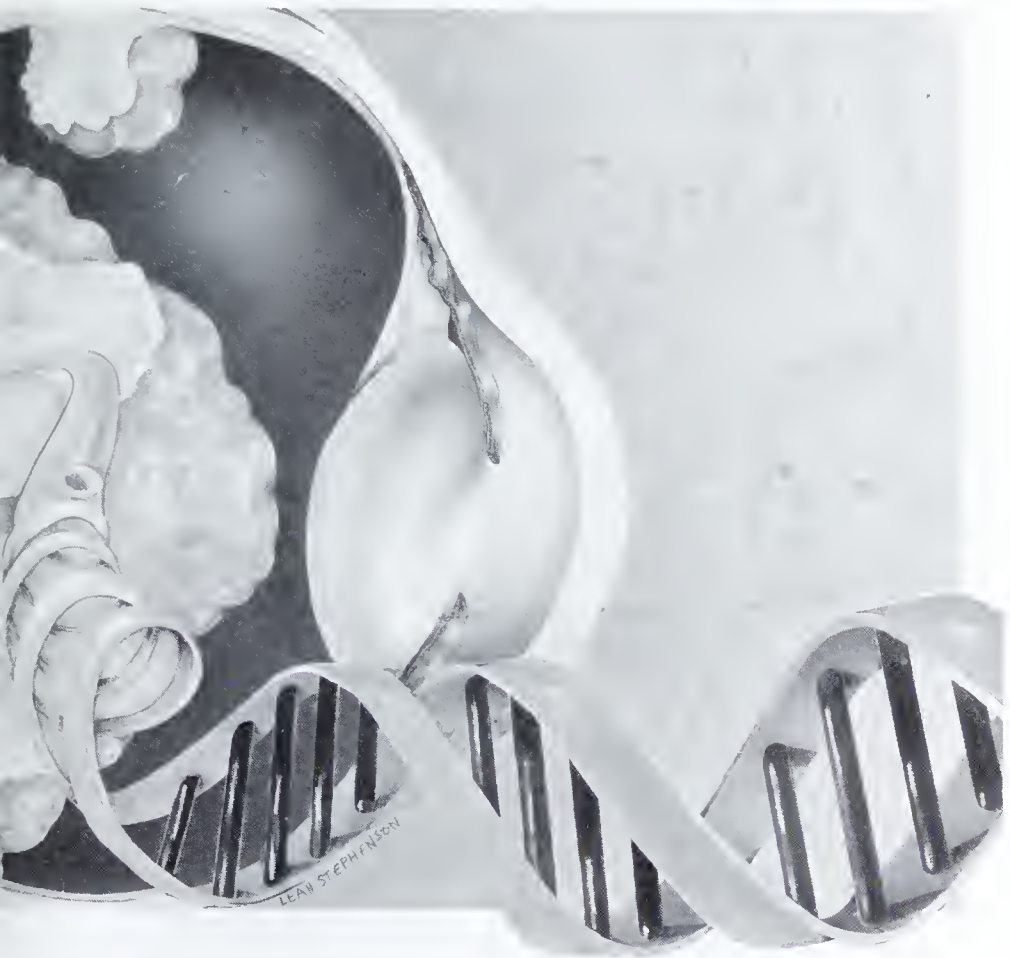
Retinoblastoma

Retinoblastoma occurs in both heritable and non-heritable forms, which can usually be distinguished clinically (Fig. 1).[7] Ten percent of all retinoblastoma patients have a family history of the disease. Another thirty percent of cases are also heritable, but have a negative family history; these individuals have acquired new germline mutations, which developed within the early embryo or within the germ cells of parent.[9] The inheritance pattern of retinoblastoma is autosomal dominant, with a penetrance of 80-90%. Heritable tumours are usually multifocal and bilateral, although some are unilateral. Non-heritable retinoblastomas are unilateral and unifocal.

Patients with retinoblastoma usually present between the ages of one and three, and almost always before the age of seven.[8] This is probably because the retina completes development at an early age, beyond which tumours do not occur.[7] Retinoblastomas can be locally invasive, but do not tend to metastasize. Effective therapy is available, and the cure rate is greater than 90%.[10] However, patients with heritable/bilateral retinoblastoma have an extremely high incidence of second, non-ocular malignancies, especially osteosarcoma.[10]

On the basis of a statistical analysis of heritable and non-heritable retinoblastoma, Knudson proposed in 1971 that development of this cancer follows two successive mutational events at both alleles of the same gene, hereafter referred to as RB.[3] In heritable cases, the first of these events occurs through development of a new germline mutation or through inheritance of a mutant RB allele; a tumour then develops after a second somatic mutation, of the normal RB allele, in fetal or infant retina. In non-heritable cases, both events take place somatically in the retina.

Molecular genetics, cytogenetics and isoenzyme studies have all supported Knudson's hypothesis. Using these techniques, the RB gene has been mapped to chromosomal band 13q14.[7,8] The molecular genetic analysis of retinoblastoma was facilitated by the isolation of DNA probes which were localized to 13q14. One



such probe, called pH3-8, was able to detect homozygous deletions in 2 out of 37 retinoblastomas, indicating that these tumours arose when both alleles of a gene from this region were inactivated.[11] The pH3-8 probe was the starting point for the eventual cloning of the RB gene (see below).

As shown in Figure 1, several types of genetic events could result in recessive inactivation of the RB gene in the developing retina. RFLP analysis has been used to determine the nature of these somatic mutations in both types of retinoblastoma. RFLPs (restriction fragment length polymorphisms) result from inherited differences in restriction endonuclease recognition sites. Retinoblastoma patients whose leukocyte DNA is informative (i.e. heterozygous) for DNA markers along the long arm of chromosome 13 usually show loss of this heterozygosity in their tumour DNA (Fig. 1).[12] This reduction to homozygosity is specific to chromosome 13, since markers from other chromosomes retain heterozygosity in informative patients. About 75% of retinoblastomas show reduction to homozygosity or hemizygosity for some portion of 13q.[9] Several chromosomal mechanisms could account for this, including mitotic recombination (Fig. 1).[12] The net effect of such events is to delete or replace the normal RB allele, since in familial cases the tumours have been shown to retain 13q alleles from the affected parent.[8]

The RB Gene

A candidate retinoblastoma gene has recently been cloned.[13-15] By cloning overlapping DNA 5′ and 3′ of the pH3-8 probe ("chromosome walking"), DNA probes were obtained which detected a 4.7 kb (kilobase) mRNA transcript in normal retinal cells. Full length cDNAs of this transcript have been cloned and sequenced, and the organization of its gene is being determined. The RB gene consists of at least 20 exons (coding segments) spread out over an estimated 200-225 kb of genomic DNA.[16]

Retinoblastomas have a high frequency of abnormalities in the structure and expression of the candidate RB gene, supporting its identification as the genuine retinoblastoma gene. Genomic abnormalities of RB, including homozygous deletion, can be detected with a cDNA probe in 30-40% of retinoblastomas[13,15], although a much lower frequency has also been reported.[17] Some tumours without obvious structural changes in the RB gene either do not express a 4.7kb transcript or express a transcript of the wrong size.[13-15,17] To screen for mutations which are not detected by Southern and Northern blot analysis, one group has used a "ribonuclease protection" assay which detects about 50% of point mutations in mRNA. Out of 11 tumours with normal 4.7 kb transcripts, 5 had mutations which were detected as abnormal ribonuclease cleavage patterns.[18] Given the limitations of this technique, these results are consistent with the hypothesis that all retinoblastomas contain mutations of RB.[18]

Alterations in the RB gene have been detected in several tumour types other than retinoblastoma. Both sporadic osteosarcomas and the osteosarcomas from patients with heritable retinoblastoma show reduction to homozygosity for 13q markers around the RB gene.[8,19] Structural changes in the RB gene have been detected with cDNA probes in a high proportion of sporadic osteosarcomas,[19] as well as in several soft tissue sarcomas.[6,20] The association between heritable retinoblastoma and osteosarcoma thus appears to be due to a shared initiating mechanism.[6]

Other tumours which have shown loss of heterozygosity on chromosome 13q include small cell lung carcinoma and carcinoma of breast.[4] Both these tumour types have abnormalities in the RB gene, although at a lower frequency than retinoblastoma and osteosarcoma.[21,22] A link between these cancers and heritable retinoblastoma has not yet been established. However, it has been shown that the mothers of children with osteosarcoma have an increased incidence of breast cancer.[23] The RB gene is expressed in a number of normal human tissues,[17,22] hence it is puzzling that inheritance of a mutant RB allele predisposes to only retinoblastoma, sarcoma, and perhaps melanoma.[10]

The RB Protein

Computer analysis of the amino acid sequence of the predicted RB protein indicates no significant homology to other known proteins.[20] To aid in its identification, anti-sera have been raised against fragments of the RB protein produced by recombinant DNA methods.[24] These antibodies recognize a protein with a molecular weight of 110-114 kilodaltons, present in cells which express normal RB mRNA. This RB protein is a phosphoprotein which is found chiefly in the nucleus. It has associated DNA binding activity, suggesting a role in the control of gene expression.[24]

To test the assumption that the RB protein can suppress tumorigenicity, the cloned RB gene has been introduced into tumour cells in which both alleles of the chromosomal RB gene were inactivated.[6] For these

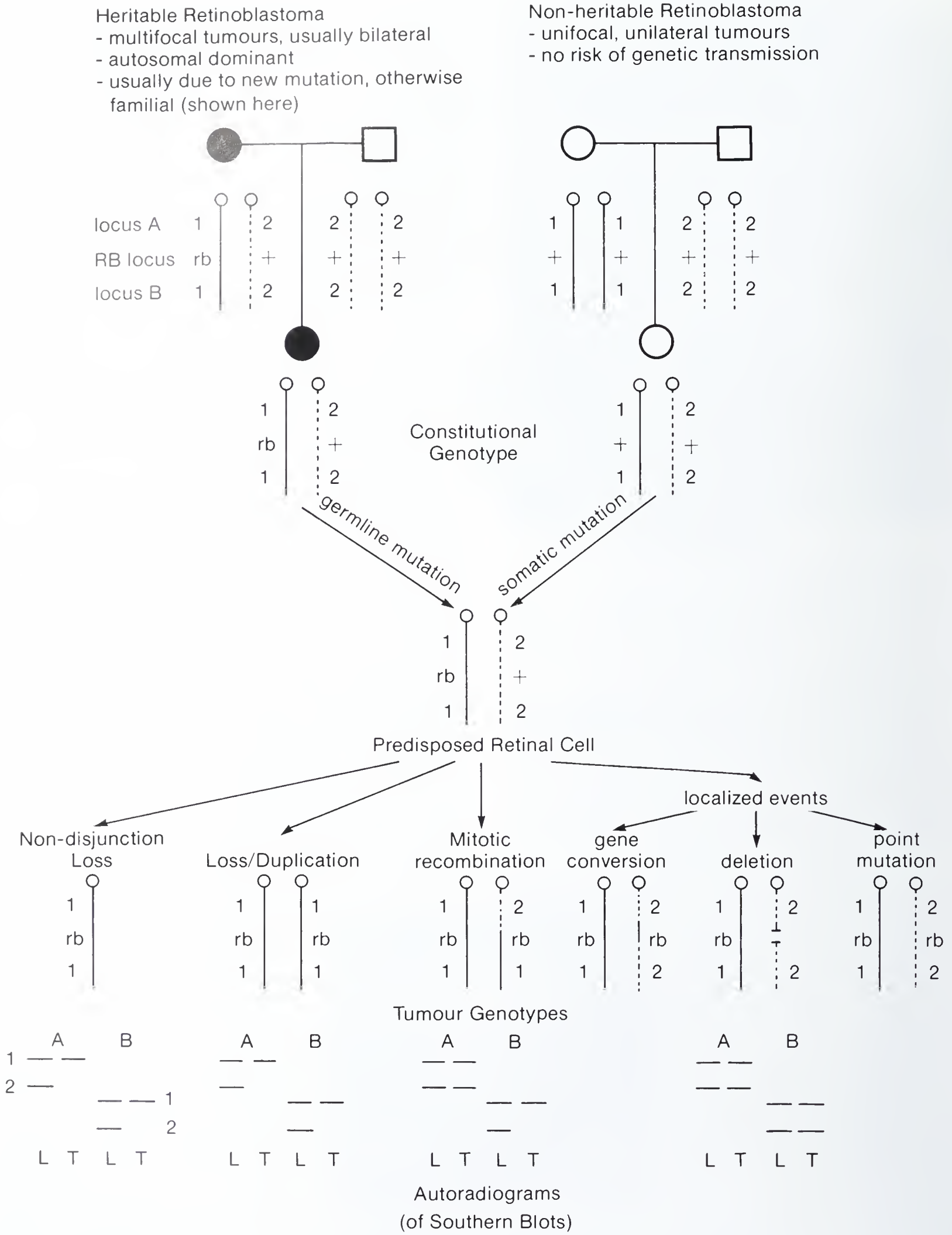


Figure 1: Genetic events leading to recessive inactivation of the RB gene in retinoblastoma. Inheritance of a mutant RB allele (rb), top left, results in a child who is rb/+ in all her cells, where + denotes the normal RB allele. In non-heritable retinoblastoma, somatic mutation of one RB allele occurs in a single retinal cell. In both situations, mutation of the remaining RB + allele can be generated by the mechanisms shown.

Genetic events which result in loss of heterozygosity at loci around the RB gene can be detected by RFLP analysis of normal (N) and tumour (T) DNA. In this example, DNA probes from both locus A and locus B detect two allelic fragments, designated 1 and 2. Somatic chromosomal events can be detected as loss of constitutional heterozygosity at one or both of these loci. Localized events, such as a point mutation, cannot by detected by this analysis (adapted from references 8 and 12).

Table 1: Regional loss of heterozygosity in sporadic tumours (not a complete list). Unless otherwise noted, data from ref. 4.

Tumour	Affected chromosomes
osteosarcoma	13q, 17p[19]
Wilms' tumour	11p13, 11p15[31]
bladder	11p
renal cell CA	3p
small cell lung CA	3p, 13q, 17p[28]
breast	11p, 13q
colon	5q, 17p, 18q[26]
stomach	13q
meningioma, acoustic neuroma	22[25]

experiments, retinoblastoma and osteosarcoma cell lines with no detectable RB protein (RB^-cells) were used. These cells were infected with recombinant retroviruses which expressed a full length RB mRNA. Appearance of the RB protein within cells correlated with a change in morphology and a decrease in growth rate. Unlike their parent cell lines, these RB+ cells were not tumorigenic in nude mice.[6] This supports the hypothesis that the RB gene is a tumour suppressor gene, and indicates that the inactivation of RB in retinoblastomas and osteosarcomas is critical for their neoplastic behaviour.

Other Tumour Suppressor Genes

The study of retinoblastoma suggested that RFLP analysis could be used to estimate the chromosomal location of other recessive cancer genes.[12] Using DNA probes from several chromosomes, investigators have screened hundreds of informative leukocyte/tumour pairs for loss of heterozygosity in tumours.[4] This approach has been extremely fruitful, and loss of constitutional heterozygosity within one or more chromosomal regions can be demonstrated in many common solid tumours (Table 1). These target regions are presumed to contain tumour suppressor genes whose inactivation is important for carcinogenesis. Such "deletion mapping"[25] has also been combined with RFLP linkage analysis to determine the location of the genes for three autosomal dominant cancer syndromes: multiple endocrine neoplasia type 1, neurofibromatosis type 2, and von Hippel-Lindau disease (Table 2). Reduction to homozygosity for markers around these loci has been found in related sporadic tumours.[4] Therefore, as in retinoblastoma, these sporadic and hereditary tumours probably develop following inactivation of both alleles of a tumour suppressor gene. At the cellular level, these genes are recessive with respect to tumour development, yet the corresponding syndromes are all inherited as autosomal dominant traits.

The genetics of some hereditary tumours is not explained by the above model,[4,26,31] in that tumour formation does not appear to follow recessive genetic change at the predisposing locus. For example, DNA markers on chromosome 5 which are linked to familial polyposis do not detect loss of heterozygosity in adenomas from patients with this disease.[26] However, some of these adenomas contain allelic deletions on chromosome 17 and 18.[26] Multiple endocrine neoplasia

Table 2: Autosomal dominant cancer syndromes, and the chromosoal location of the corresponding susceptibility genes. Unless otherwise noted, data from reference 4.

Syndrome	Predominant tumours	Chromosome
Retinoblastoma	retinoblastoma, osteosarcoma and other sarcomas, ?[10]	13q14
Familial polyposis coli	colonic carcinoma, adenomatous polyps	5p
MEN 1 (multiple endocrine neoplasia type 1)	tumours or hyperplasia of parathyroid, pituitary or pancreatic islets	11q
MEN 2 (multiple endocrine neoplasia type 2)	pheochromocytoma, medullary CA of thyroid, parathyroid hyperplasia	10
Neurofibromatosis type 1 (VRNF)	Schwann cell tumours, pheochromocytoma	17
Neurofibromatosis type 2 (BANF)	bilateral acoustic neuromas, meningiomas	22q
von Hippel Lindau disease	renal cell CA, retinal and cerebellar hemangioblastomas, pheochromocytoma	3p
Wilms' tumour	Wilms' tumour	11p13, ?[31]

type 2 shows linkage to markers from chromosome 10, yet these same markers do not detect loss of heterozygosity in tumours. In fact, tumours in MEN type 2 have frequently lost alleles from another chromosome, chromosome 1p.[4]

Tumour progression is thought to be driven by sequential genetic and epigenetic[27] changes which involve both proto-oncogenes and tumour suppressor genes.[26] This genetic damage appears to accumulate during the clonal evolution of tumours, resulting in progressively more malignant disease. Multiple genetic lesions can often be detected in the same tumour sample.[26,28] For example, concerted loss of heterozygosity on chromosomes 3p, 13q, and 17p has been detected in certain small cell lung carcinomas;[28] in some cases these abnormalities appeared to be followed by amplification of the N-Myc proto-oncogene. Amplification, and hence overexpression, of the Myc proto-oncogenes, (L-Myc, c-Myc and N-Myc) is a common event in small cell lung cancer, and appears to correlate with more aggressive disease.[29] A similar correlation has been made for N-Myc amplification in neuroblastoma.[30] Some genetic events occur relatively early in the progression of human tumours,[26] whereas other events, such as gene amplification, have been shown to occur in more advanced lesions. The detection of this genetic damage may eventually complement existing techniques for the staging of tumours.

Perspectives

The cloning of the retinoblastoma gene is one of the

first successes of "reverse genetics", the process whereby a gene is cloned solely on the basis of chromosomal location and involvement in human disease.[32] DNA probes from within the RB gene will be useful in the genetic counselling of retinoblastoma patients and their families.

The cloned RB gene can suppress the neoplastic growth of tumour cell lines.[6] However, it has yet to be shown directly that inactivation of the RB gene leads to malignancy. Creation of an animal model of retinoblastoma would be useful in this respect, and powerful techniques exist for the creation of such a strain.[33,34] For example, it is now possible to create transgenic mice which contain defined mutations within specific genes.[33] The study of mice with both heterozygous and homozygous RB mutations would help clarify the role of the RB gene in both carcinogenesis and normal development.

At the biochemical level, the RB protein has been localized to the cell nucleus, where it may control the expression of other genes.[24] Potential functions for the RB protein include a role in the cellular response to factors which inhibit normal cell proliferation, such as transforming growth factor-beta.[35] The RB protein has recently been shown to interact with the oncogene products of several DNA tumour viruses including HPV-16 (human papillomavirus type 16),[36] which has been linked to human cervical carcinoma. Although the functional relevance of this interaction is not clear, these tumour viruses could transform cells by biochemical inhibition or inactivation of the RB protein. It will be interesting to see if the RB protein interacts with the gene products of cellular proto-oncogenes, specifically those of the Myc family.[36]

With the cloning of the retinoblastoma gene, the existence of human tumour suppressor genes moves out the realm of conjecture. The use of RFLP analysis in tumour genetics, pioneered in the study of retinoblastoma,[12] has identified the chromosomal location of numerous potential tumour suppressor genes. The molecular identification of these genes will likely have a major impact on the understanding of human cancer, and will hopefully aid in the development of more specific treatment strategies.

Acknowledgements

I would like to thank Anne Koch, Dr. Brenda Gallie and Dr. Katherine Paton for helpful comments on the manuscript, and Andrew Cunningham for help with his word processor.

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Pre-eclampsia - The Disease of Theories

Candice Benjamin, 9T0

Abstract

Pre-eclampsia is the leading cause of maternal mortality in developed countries and is associated with an increased risk of foetal mortality and morbidity. Although its etiology and pathophysiology is not completely understood, recent studies have shed some new light on it. The most recent studies implicate dietary deficiency of calcium as a cause of pre-eclampsia.

Pre-eclampsia is a significant complication of pregnancy in that it is the leading cause of maternal mortality in developed countries. It is also associated with an increased incidence of foetal and neonatal mortality and morbidity. Pre-eclampsia has been described as the disease of theories. It was stated by two leading authorities on pre-eclampsia, Gant and Worley, that;

"...the number of theories advanced to explain the etiology and pathophysiology of pre-eclampsia is limited only by the supply of investigators and their access to strong drink."[1]

This gives some indication as to the multiplicity of ideas surrounding the pathophysiology of this entity. Pre-eclampsia has been recognized as a clinical entity since 1739 but confusion about how to diagnose it still exists today in the literature. This is, in part, due to the poor understanding of its etiology and pathophysiology, but also to the lack of standardized clinical tests and pathological features that can be used in its diagnosis. This paper addresses the issue of how to correctly diagnose pre-eclampsia and outlines the current ideas of its pathophysiology.

Classification

A new classification of hypertensive disorders in pregnancy has been introduced to standardize the terms used by clinicians.[2] According to this, pregnancy induced hypertension, a term that was used synonymously with pre-eclampsia, has been redefined. Pregnancy induced hypertension is defined as hypertension in pregnancy commonly, but not exclusively, found in primigravid women. Apart from the hypertension there is no evidence of disease in other systems. When the blood pressure is very high the risk of placental abruption and maternal stroke is increased. The major significance of pregnancy induced hypertension (P.I.H.) is that it leads to pre-eclampsia if it is severe.[3] Pre-eclampsia is referred to as gestational proteinuric hypertension in the new classification. That is, significant proteinuria accompanying hypertension which can occur antenatally, during labour or in the puerperium of a previously normotensive, non-proteinuric woman.[2] Excessive weight gain can be seen in pre-eclampsia. This is due to fluid retention and oedema which is facial or in the hands. The presence of oedema is not needed to make the diagnosis of pre-eclampsia. The hypertension and proteinuria must be present after the twentieth week gestation.

Predisposing factors are diabetes mellitus or renal

disease, hydatidiform mole, multiple pregnancy and hydramnios. Teenagers and primigravidas as well as those of advancing maternal age are at increased risk of developing the disease.[4] Pre-eclampsia carries with it a high risk of maternal mortality and foetal mortality and morbidity. The latter is related to the complications of intra-uterine growth retardation, resulting from poor circulation to the placenta, and of premature delivery which may be spontaneous or induced in the interest of maternal health. Pre-eclampsia can progress to eclampsia.

Eclampsia is defined as the occurence of generalized convulsions during pregnancy, labour or within seven days of delivery, not caused by epilepsy or other convulsive disorders.[2]

Diagnosis:
Hypertension

In a normal pregnancy, the blood pressure undergoes certain changes. The systolic and diastolic pressures decrease by 4-6 mmHg and 8-15 mmHg respectively. The blood pressure reaches its lowest value, typically 105/55 mmHg,[3] by twenty to twenty-four weeks gestation. It gradually increases during the third trimester and reaches pre-pregnancy values by the time of delivery.[5] There are two criteria commonly used for diagnosing hypertension:

1) An absolute blood pressure of 140/90 mmHg on two occasions, separated by at least six hours, after the twentieth weeks of gestation.
2) A relative rise in blood pressure over first trimester values of $>$ 30 mmHg systolic or $>$ 15 mmHg distolic after the twentieth week of gestation.[5]

The latter criterion poses some difficulties. Poor documentation of blood pressure before pregnancy or in early pregnancy is common. This means that there are many pregnancies in which there is no reference value from which to calculate the rise. A second problem is that blood pressure changes markedly in early pregnancy. It can be difficult to know at what point in the pregnancy the blood pressure should be considered to be a baseline. A final problem is that blood pressure increases during the third trimester anyway. The sensitivity of a systolic rise of $>$ 30 mmHg in predicting pre-eclampsia is 6.8 - 22.7% and the sensitivity of a 15 mmHg rise in diastolic pressure in predicting pre-eclampsia is 20.5 - 52.3%. For these reasons the second criterion should not be used in diagnosing pre-eclampsia.[6]

It has been shown that an absolute blood pressure of

140/90 mmHg correlates best with foetal and maternal prognosis and with the development of proteinuria.[2]

Summary

Pregnancy induced hypertension is defined as an absolute blood pressure of 140/90 mmHg on two occasions separated by at least six hours, after the twentieth week of gestation.

Proteinuria

Pre-eclampsia is defined as P.I.H. plus proteinuria. Proteinuria can be measured by dipstick or the sulfosalicyclic acid cold test on a random urine sample. The results of a random urine sample protein assay are unreliable because it varies with contamination, exercise or changes in posture. The best method for measuring protein in the urine is to use a 24 hr total urinary excretion, with significant proteinuria defined as > 300 mg/24 hrs.

Diagnosis of pre-eclampsia:

Pre-eclampsia is divided into mild and severe forms as shown in Table 1.

Table 1

	Blood pressure	Proteinuria
Mild	140/90 - 160/110 mmHg	0.5 - 5 gm/24 hrs 1-2+ dipstick
Severe	> 160/110 mmHg	>5 gm/24 hrs 3-4+ dipstick

Severe pre-eclampsia is also diagnosed when mild pre-eclampsia is complicated by multisystem disease. Table 2 indicates the possible presentation of pre-eclampsia in different organ systems.

Table 2

1. Renal	- proteinuria is a manifestation of renal disease. - elevated serum urate is the added finding in severe cases. - oliguria (< 400 ml/24 hrs)
2. Respiratory	- pulmonary oedema ± cyanosis.
3. Abdomen	- epigastric or right upper quadrant pain. - abnormal liver function tests.
4. Brain	- altered consciousness, headache, scotoma, blurred vision, hyperreflexia.
5. Blood	- thrombocytopenia (hallmark of disseminated intravascular coagulation - D.I.C.).

Pathogenesis of Pre-eclampsia

The next section outlines three major findings in pre-eclampsia and examines the current explanations for them.

Increased Vasomotor Tone

It was recognized in the 1960's, by various studies, that normotensive pregnant women exhibited decreased responsiveness to infused vasoactive agents than non-pregnant women. Gant et Al[1] found pregnant women to be less responsive to infused angiotensin II (AII) than were their non-pregnant counterparts. However, those that went on to develop pre-eclampsia gradually lost this refractoriness from the 18th week of gestation onward. By the 32nd week of gestation their sensitivity to AII was found to be greater than that of non-pregnant controls. This suggests that pre-eclampsia is characterized by a loss of refractoriness to vasoactive agents from the middle of the second trimester onwards. Although signs of pre-eclampsia may resolve with treatment, the sensitivity to vasopressor agents does not go until after the baby is delivered.[1]

Investigators have looked at the possibility that the levels of vasoactive agents may be greater in the pre-eclamptic patients, thus contributing to the increase in vasomotor tone. Studies fail to show any significant difference between renin and angiotensin levels in the pre-eclamptic women versus normotensive pregnant women. Two studies were conducted to look at the level of angiotensin converting enzyme in pre-eclamptic and normotensive pregnant women. The reports from these were conflicting.[7,8] In view of this information, the renin-angiotensin system does not seem to contribute to the development of increased vasomotor tone. The suggestion is, therefore, that the elevated blood pressure is a result of increased responsiveness of the vessel wall to vasoactive substances in the circulation.[9]

The question that arises is - what is responsible for this increased responsiveness of the vessel walls to vasoactive agents? The current theory is that this is due to increased intracellular accumulation of calcium ions which sensitizes the vascular smooth muscle to constrictor stimuli.[1] Several studies have surfaced in support of this theory. Lopez-Jaranillo et Al.[10] have demonstrated, in a double blind study, that when 2 mg of calcium is supplemented to the diet of primigravid women the incidence of P.I.H. is statistically lower than in those who weren't supplemented. Kawasaki et Al.[11] have demonstrated that calcium supplementation decreases vascular sensitivity to AII. In order to explain these findings one must look at calcium metabolism during a normal pregnancy. During pregnancy, the demand for calcium increases because of foetal requirements. The foetus accumulates a total of 30 gm of calcium during the pregancy, 80% of which are acquired during the third trimester, therefore the mother loses a lot of calcium to the foetus. Maternal bone calcium is preserved during pregnancy because of decreased response of these cells to parathyroid hormone (PTH), but total and ionized calcium levels decrease in the serum during pregnancy, especially in the third trimester. This results in increased PTH levels in the serum. PTH causes calcium ions to enter certain cells, such as kidney, liver and HeLa cells. A report has not been written on the effect of PTH on smooth muscle cell calcium ion concentrations. Presumably a diet that does not meet the foetal demands for calcium will result in a

state of physiological hyperparathyroidism. A study designed to investigate whether PTH does increase calcium ions in vascular smooth muscle cells is needed for this theory to gain more strength.

Abnormal Prostaglandins

Prostaglandins affect the responsiveness of vascular smooth muscle to pressor agents.[1] Normal vascular tone depends on a balance between the production of those prostaglandins which increase vascular tone and those that decrease it. Endoperoxides can go on to form prostaglandins, prostacyclin or thromboxane A2. Thromboxane A2 (TxA2) is a powerful vasoconstrictor which is generated by platelets. Prostaglandins E2 (PGE2) is a powerful vasodilator as is prostacyclin (PGI2). PGI2 is formed by vascular endothelial cells. In pre-eclamptic women PGE2 and PGI2 levels are decreased. Some investigators have looked at the effect of prostaglandin synthetase inhibitors, such as indomethacin and aspirin, on the vascular response to infused AII. It was found that indomethacin and, to a lesser extent, aspirin increased the responsiveness of the vessel walls to infused AII.[1] This suggests that prostaglandins are responsible, in part, for the acquisition of vessel wall refractoriness seen in normal pregnancies.

Since prostaglandin deficiency can reproduce the finding common to all pre-eclamptic patients, studies have begun to look at whether pre-eclampsia is due to a deficiency of prostaglandin precursors. This was found to be the case in pregnant rabbits but not in humans. Effort is now directed to search for abnormalities in the synthesis of prostaglandins. In the interest of treatment possibilities, investigators have also begun to look for agents that will selectively inhibit TxA2 synthesis or increase PGI2 production. Low dose aspirin (40-50 mg/day)[1] was found to increase the synthesis of PGI2 selectively. The doses of aspirin required to inhibit prostaglandin synthesis are much higher than this. More evidence is required before such a regimen should be advocated.

Abnormal coagulation

D.I.C. is seen in severe pre-eclampsia. D.I.C. is an acquired thrombohaemorrhagic disorder than can occur as a complication of many diseases. It can be triggered by a) the release of tissue thromboplastin into the circulation or b) widespread endothelial cell injury which initiates the intrinsic pathway of coagulation. Once the coagulation system has been initiated microthrombi form in the vessels throughout the body. As a result, there is consumption of the coagulation factors, platelets, fibrin and activation of the fibrinolytic mechanism. D.I.C. can present with signs and symptoms of tissue hypoxia or infarction due to the microthrombi impairing tissue perfusion. It can also present as a haemorrhagic diathesis related to the consumption of the elements needed for clotting. This haemorrhagic diathesis is aggravated by the activation of the fibrinolytic system.

In a normal pregnancy there is an increase of all coagulation factors, except factor XIII, and a shortening of the prothrombin time such that one has an accelerated state of coagulation. D.I.C. rarely occurs, however, because there is a high concentration of inhibitors of coagulation, such as antithrombin III, in the serum. If thrombin is formed it will combine with antithrombin III to form a complex called thrombin-antithrombin III (TAT). High serum TAT levels herald the presence of an accelerated state of coagulation which does not result in the formation of thrombi because the coagulation is halted prematurely. A study which looked at the levels of TAT, antithrombin III, fibrin degradation products (FDP) and platelets in the serum of normotensive and pre-eclamptic pregnant women, was performed.[12] TAT, only, was found to be increased in pregnant women who were normotensive. This confirms that pregnancy is associated with increased coagulation. Pre-eclamptic patients were found to have low TAT, low antithrombin III, low platelets and low FDP levels in their serum. In D.I.C. there are high levels of TAT and FDP and low levels of platelets and antithrombin III. The picture in pre-eclampsia is compatible with D.I.C. except for the low TAT levels. An explanation for this is that there is chronic consumption of antithrombin III such that the thrombin, formed by the accelerated coagulation, cannot be complexed to form TAT. TAT levels are therefore lower. Thus, any new thrombin formed in the circulation will result in a consumption of the coagulation factors such that D.I.C. may develop. This study suggests that pregnancy, pre-eclampsia and D.I.C. are a continuum of accelerated coagulation with pregnancy and D.I.C. at the extreme ends. Pre-eclampsia is at the point on the continuum where compensatory mechanisms for the accelerated coagulation of preg-nancy are beginning to fail. From this, a high TAT level alone was not considered to be a marker for imminent pre-eclampsia, but when associated with low antithrombin III levels it was. It has been suggested that antithrombin III serum levels could be used to monitor the development of pre-eclampsia. More research is needed in this area to see if it is feasible.

Saleh et Al.[13] have developed a theory which provides a good explanation for the findings in pre-eclampsia. This group have followed markers for endothelial cell damage, fibronectin, as well as markers for coagulation and fibrinolysis during pregnancy and in the puerperium. They found that fibronectin levels were highest in the serum of pre-eclamptic women and that the resolution of pre-eclampsia upon delivery of the baby was more closely associated with the fibronectin levels than with the other parameters. This implicates endothelial cell damage as the central disturbance in pre-eclampsia. Their theory suggests that vascular cell damage activates the clotting mechanisms via the intrinsic pathway and activates the fibrinolytic pathway be increasing plasmin levels. The low molecular weight peptides formed by fibrin degradation can lead to further endothelial cell damage and vasospasm (increased blood pressure). The thrombin formation activates platelets which then release TxA2 and serotonin. These also cause vasospasm. Thrombin consumes antithrombin III such that fibrin is formed and deposited in the vessels, hence occluding them. PGI2 is

produced by vascular endothelial cells, hence damage will result in decreased PGI2 production. Endothelial cell injury also results in protein leak into the interstitial space which contributes to the formation of oedema. This theory explains all of the findings seen in pre-eclampsia. The high vasomotor tone results from increased TxA2 and serotonin production by activated platelets and from decreased PGI2 production. The abnormal prostaglandin findings are explained above. The abnormal coagulation is explained by initiation of coagulation secondary to widespread endothelial cell damage. The question to be answered is - what causes this endothelial cell damage? Saleh et Al. postulate that it is due to immune complex deposition or to vasospasm. These answers are very unsatisfactory in that it brings one no closer to an understanding of the etiology than before. Recent studies, Rodgers et Al.[14] in San Francisco, California have reported that serum from pre-eclamptic women is cytotoxic to endothelial cells in vitro. This cytotoxicity was reduced after 24-48 hours postpartum. Pre-eclampsia may well be caused by a "toxin", despite the fact that it has fallen out of favour as a putative etiologic agent.

The aim behind these efforts to better understand the pathophysiology of pre-eclampsia is to allow prevention and treatment. The main goal in treating pre-eclampsia is to reduce maternal mortality and morbidity due to cerebrovascular accidents, and to decrease perinatal morbidity and mortality due to intrauterine growth retardation, placental infarcts and placental abruption.

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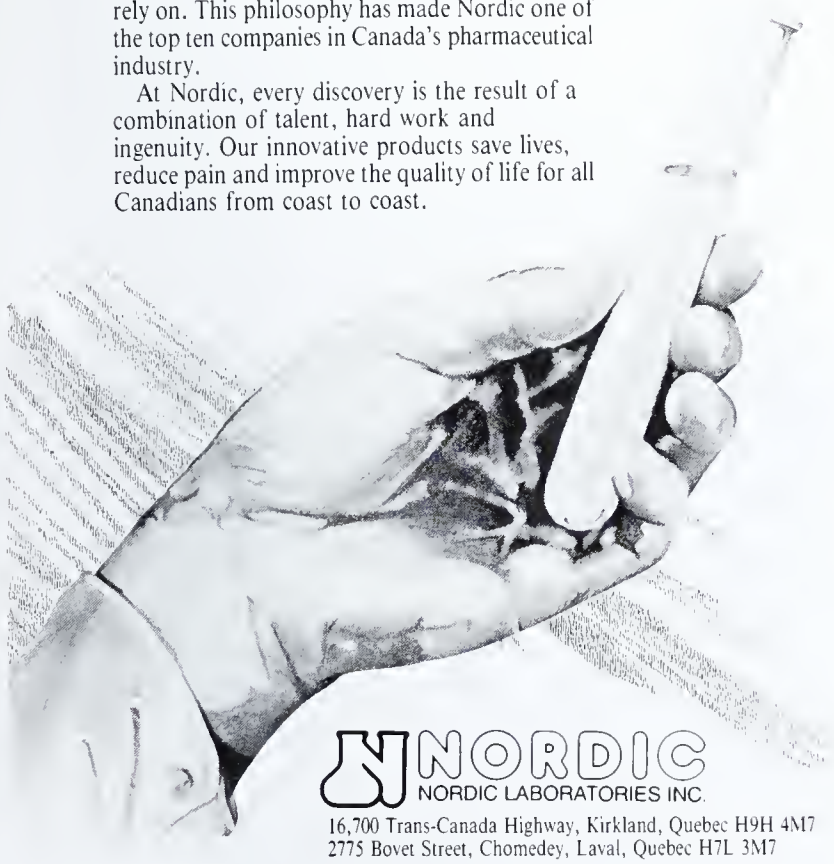

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Ultrasound in Obstetrics and Gynecology

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Introduction

Ultrasound imaging is the use of high frequency sound in the order of several megahertz, to image internal structures by the differential reflection of signals produced when a beam of sound waves is projected into the body and bounces back at the interface between structures.

It offers an advantage over radiologic imaging because no ionizing radiation is involved. Thus, it plays a major role in Obstetrics and Gynecology as a relatively safe way to image the developing fetus.

Currently, ultrasound is a routine part of antenatal care in most centres, and is a valuable tool in dating pregnancies, screening for abnormalities of development, and in the diagnosis of fetal, placental and maternal pathology.

This section will present three cases in order to introduce some of the applications of ultrasonography in Obstetrics and Gynecology and to familarize the reader with their interpretation.

Case One

Mrs. H.K. is a 28 year old G-4, P-3, who presented with painless, bright red vaginal bleeding of three hours duration in her twenty sixth week of gestation. The bleeding was moderate and she had used only one sanitary maxipad. The bleeding started when she was at rest and she denied any straining or heavy work in the last few days. The first day of her last normal menstrual period was January 15, 1987, making her expected day of confinement October 22, 1987. She was not using any form of birth control prior to this pregnancy and had been on the birth control pill for two years from the age of nineteen to twenty one.

This pregnancy had been uneventful to this point with no pain or bleeding. She had been visiting her doctor monthly, had never smoked and had consumed no medication or alcohol throughout this pregnancy.

Her previous pregnancies had been uneventful except for the third in which a C-section was performed for reasons unknown to the patient. She said that there was some sort of "blockage" of the birth passage at that time.

Family history was negative and a review of symptoms was non-contributory.

On examination the patient was a healthy looking

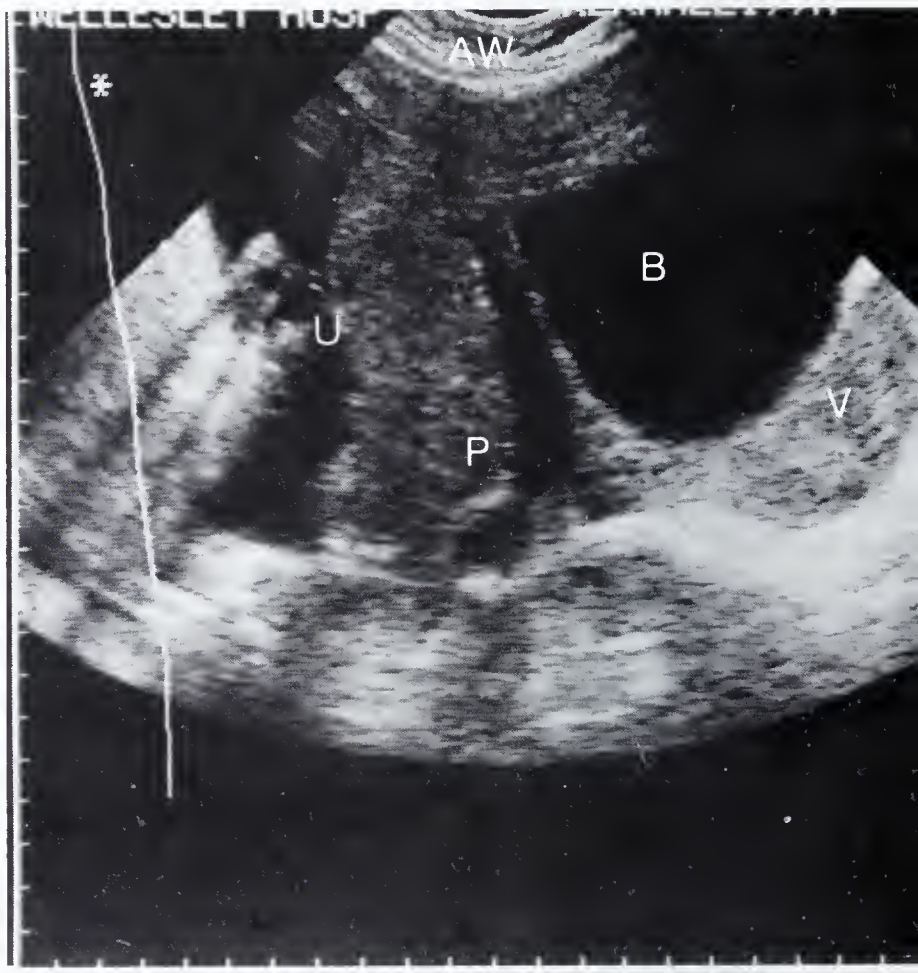

Figure 1. (AW) abdominal wall, (V) vagina, (B) bladder, (U) uterus, (P) placenta

pregnant female, looking her stated age and in no distress. The vital signs were: heartrate of 95 beats per minute; blood pressure of 125/ 80 mm Hg, right arm in the sitting position; and a respiratory rate of 13 breaths per minute.

Abdominal examination revealed a fullness consistent with pregnancy with a symphysis-fundal height of 27 cm. The uterus was non-tender and non-irritable. The fetus was easily outlined and in a transverse lie. On examination of the external genitalia, bright red blood was observed on the labia majora and labia minora. Speculum and digital examination were deferred.

A fetal heartbeat was detected by Doppler and a non-stress test was normal.

An ultrasound was ordered.

1. What is your differential diagnosis of painless vaginal bleeding during late T-2, early T-3?
2. What is your diagnosis based on the ultrasound?

Case Two

Mrs. L.B. is a 39 year old female, G-5, P-4, of Chinese background, who was born in Hong Kong. She presented to the Emergency Room with dark brown vaginal bleeding associated with no pain, but with some crampy discomfort in her lower abdominal area. The bleeding had started approximately twenty four hours previous and she had used five sanitary maxipads. The first day of her last normal menstrual period was approximately February 16, 1988, which would date this pregnancy at thirteen weeks and make her expected date of confinement November 23, 1988. She had never used any form of contraception.

She had not seen her family doctor regarding this pregnancy. This pregnancy had been associated with daily nausea and vomiting. The patient also complained of some "dizziness", which was described as "feeling light headed", of two weeks duration, and a general increase in the level of anxiety for the last month.

Her previous pregnancies had been uneventful and each ended in a spontaneous vaginal delivery at full term.

Family history was negative.

The patient took no medications during this pregnancy, and drank no alcohol. She had a fourteen pack year history and had continued to smoke through this pregnancy.

A review of systems was non-contributory.

On examination the patient appeared pale and in distress. The vital signs were: a heart rate of 100 beats per minute; blood pressure of 145/ 95 mm Hg. right arm in the sitting position; and a respiratory rate of 18 breaths per minute.

Abdominal examination revealed a symphysis - fundal height of 20 cm. The uterus was soft and non-tender. A fetus could not be outlined. Pelvic examination revealed normal external genitalia; a normal vaginal canal and a

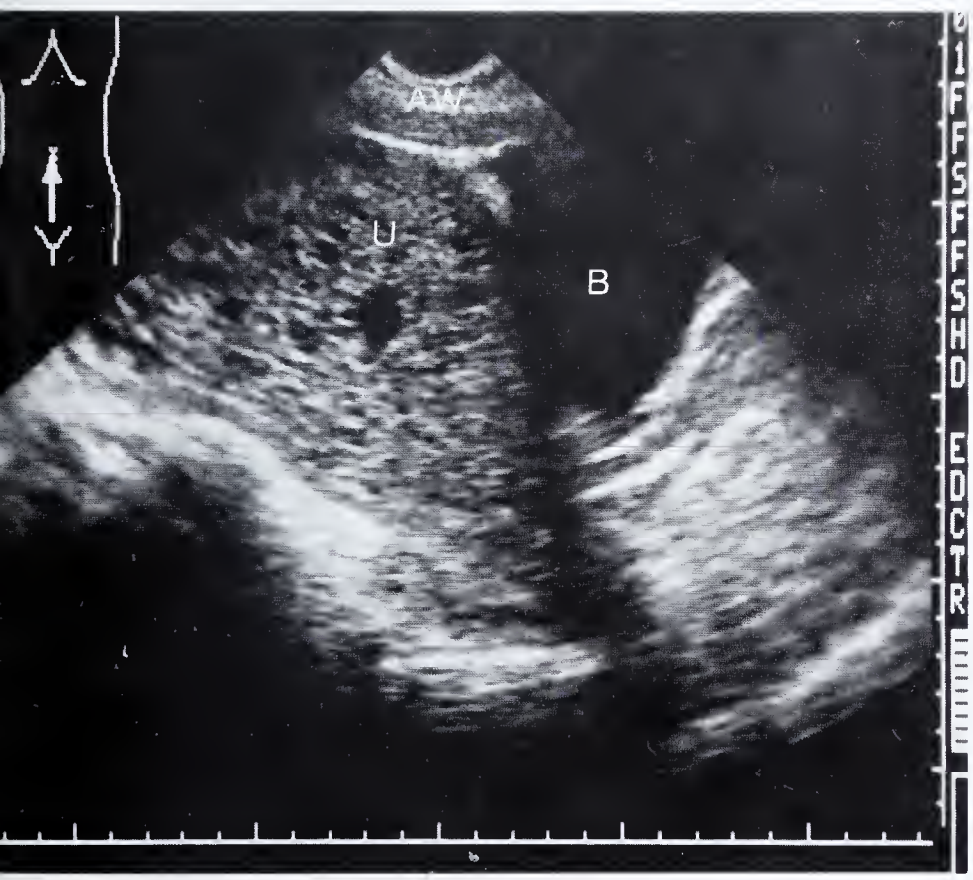

Figure 2: (AW) Abdominal Wall, (B) Bladder, (U) Uterus

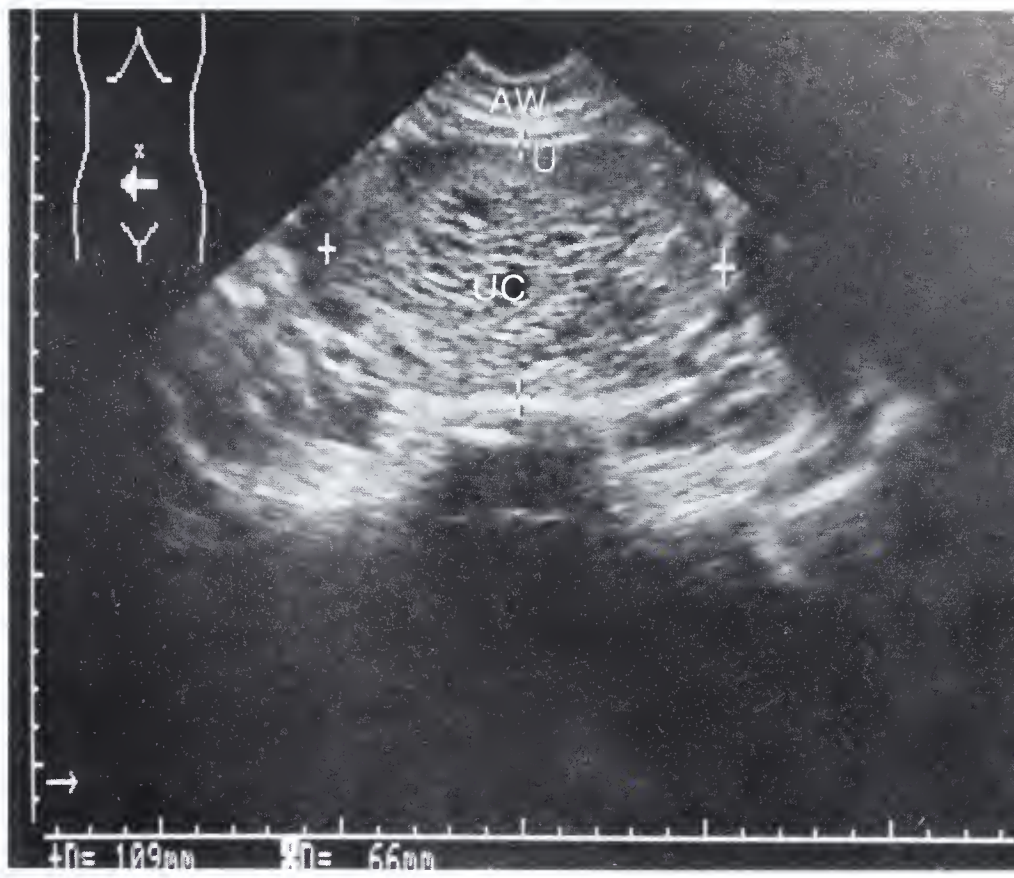

Figure 3. (AW) Abdominal Wall, (U) Uterus, (UC) Uterine Contents

cervix free of lesions visible with the naked eye. The cervical os was closed. There were traces of brown blood throughout these structures. No fetal heart could be located by Doppler. An ultrasound was ordered.

1. What does the ultrasound show?
2. What is your diagnosis?

For answers to questions see page 46.

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Researching the Future

Cardiac and Pericardial Calcification

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From the Departments of Radiology and Medicine, The Wellesley Hospital

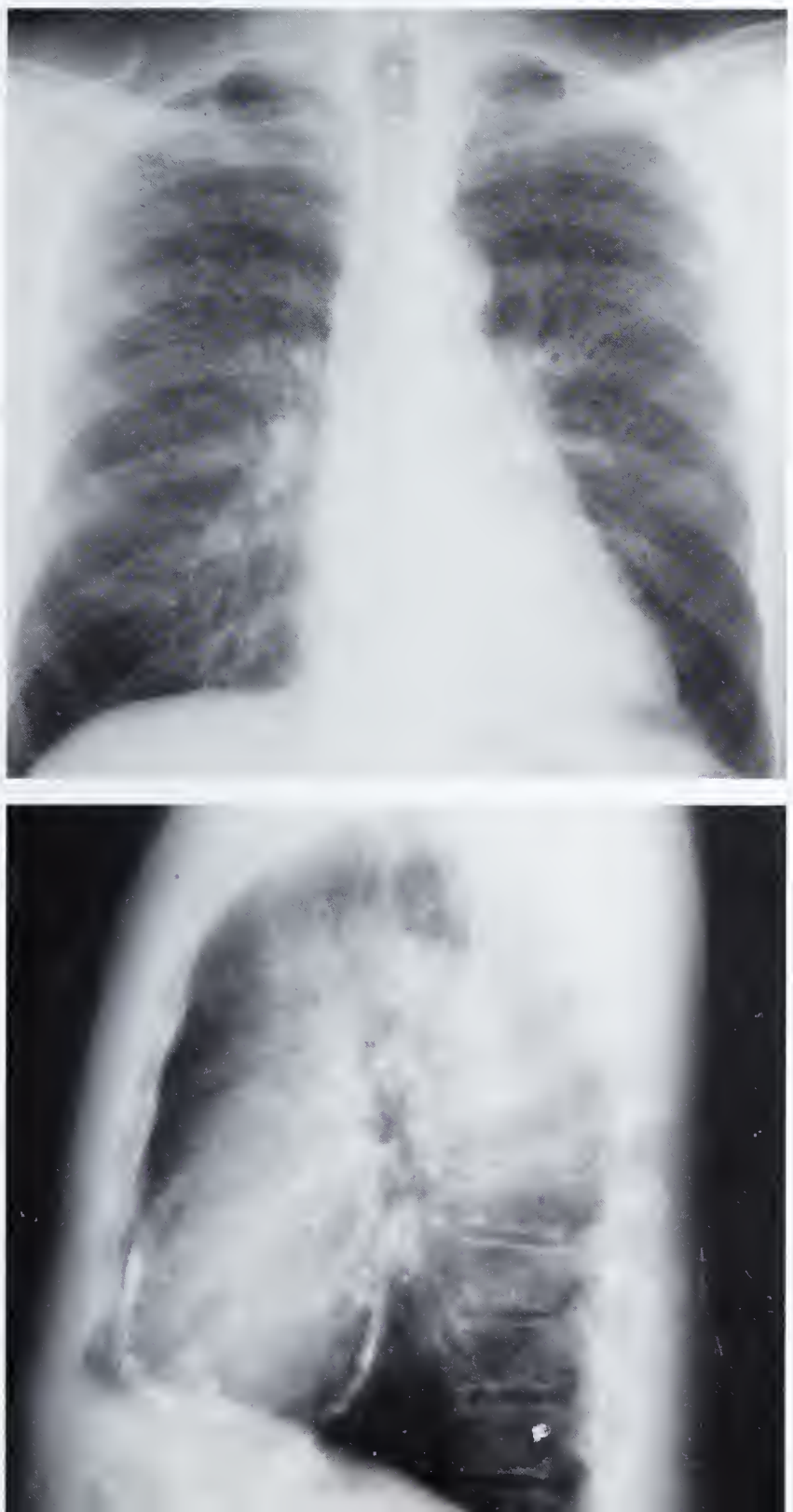
Abstract

The radiologic detection and understanding of cardiac and pericardial calcifications on a patient's radiograph is an important part of clinical practice. The location of these calcifications within the heart is varied and essential in assessing their significance. This paper reviews the etiologies and clinical significance associated with the various heart calcifications detectable on a chest radiograph.

The heart is principally composed of muscle surrounding blood filled chambers with a thin tissue envelopment, all being of similar radiographic density. On a chest x-ray it appears as a homogeneous mass in the thorax much more radiodense than the air containing lung surrounding it. Occasionally, within the structure of the heart, collections of calcium or bone dense deposits are detected against the homogeneous fluid dense background of the cardiac shadow on a chest x-ray.

Calcifications have been reported in the hearts of greater than 80% of people older than age 40 examined at autopsy.[1] Calcification most commonly involves the coronary arteries, pericardium, mitral and aortic annuli, left atrium, cardiac valves, and myocardium; separate radiological and clinical pictures are associated with these different anatomical sites.

Figure 1: Pericardial calcification. A densely calcified pericardial band (best seen on the lateral view) outlines the diaphragmatic and posterior surfaces of the heart and extends into the A-V groove.



Pericardial Calcification

Pericardial calcification can be caused by many different etiologic factors. The most common are Rheumatic heart disease, trauma, tuberculosis and histoplasmosis. Generally calcium is deposited in the pericardium as a thin plaque or as a longer curvilinear layer following the cardiac contour. The calcifications are most commonly located in the atrioventricular grooves and in the lower and diaphragmatic portions of the pericardium.[2] (Fig. 1) Clinically, pericardial calcifications are an important sign of constrictive pericarditis and are considered diagnostic in any symptomatic patient. They are evident on the chest x-rays of 1/3 of patients with constrictive pericarditis but are not pathognomonic on their own for the condition and can be present at times without any constriction or functional cardiac abnormality.[3]

Valvular Calcifications

The four valves are best observed on the lateral chest x-ray and have classical positions in relation to the heart shadow (Fig. 2). The main causes of valvular calcification are Rheumatic valvular disease, congenital anomalies, bacterial endocarditis and atherosclerosis.

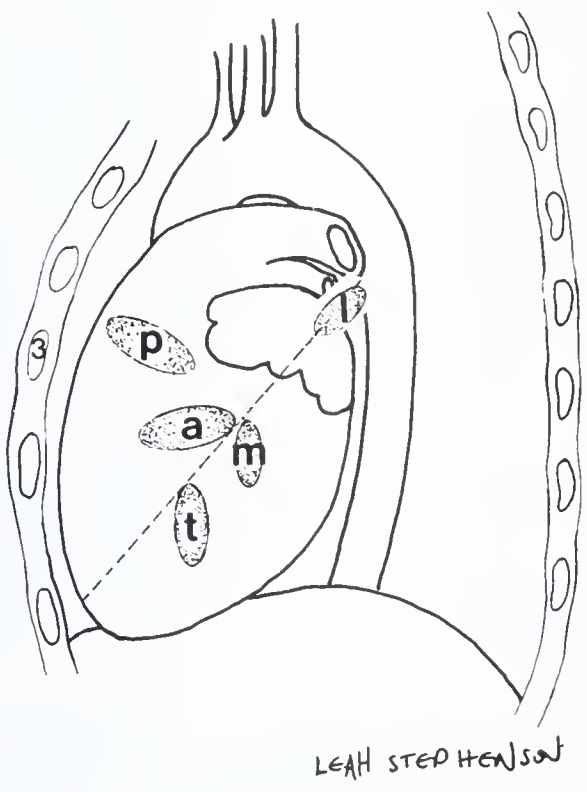


Figure 2: Classical Projection of the cardiac valves on a lateral chest radiograph (A) aortic valve, (M) mitral valve, (P) pulmonary valve, (T) tricuspid valve, (L) left upper lobe bronchus.

Mitral valve calcification is almost always due to Rheumatic fever. Calcification of the valve is more common in men and increases in incidence with age.[4] On x-ray examination of patients with mitral valve calcification the degree of involvement is quite variable, ranging from a few flattened plaques to complete valve involvement. In certain cases the calcification may also extend and infiltrate tissues such as the valve ring or annulus and rarely into adjacent myocardium.[4] Clini-

Figure 3: Mitral and aortic valvular calcification. On the lateral view the proximity between the upper aortic valve (Black arrow) and the lower mitral (White arrow) is clearly appreciated.

cally mitral valve calcifications are usually associated with mitral stenosis in association with mitral insufficiency.[3] Mitral calcification with pure mitral stenosis is quite rare.

Calcification of the mitral valve may also occur in combination with aortic valve calcification (Fig. 3). This situation is almost solely due to Rheumatic heart disease. Isolated aortic valve calcification on the other hand is usually secondary to a congenital abnormality of the aortic valve. In patients older than age 60, however, calcification of the aortic valve and ring may also occur by an atherosclerotic process.[3] The calcification observed in the aortic valve is often quite extensive and spread of the calcification into the valve ring, aortic annulus and even the mitral annulus may occur. Clinically the finding of aortic valve calcification is diagnostic of aortic stenosis of some degree,[5] except in the elderly where calcification may be associated with functionally insignificant stenosis.[4]

In contrast to the mitral and aortic valves, calcification of the pulmonic and tricuspid valves is very rare and only a few isolated cases have been reported.[3]

Mitral and Aortic Annulus Calcification

The mitral and aortic annuli are structural rings serving as the fibrous skeletons for their respective valves. They appear in the heart shadow in similar positions to that of their corresponding valves.

Calcification in the mitral annulus is due to a degenerative process associated with aging and is rarely seen in individuals younger than 60 years of age.[3] The mitral annulus is horseshoe shaped with its open aspect adjacent to the aorta. Therefore, calcification of the annulus appears J- or C-shaped due to its open medial side (Fig. 4). The calcification is usually homogeneous and quite extensive in contrast to calcification of the valve which is more irregular and less massive. The calcification is usually of no clinical significance. Rarely, severe calcification may deform the mitral orifice and result in functional impairments such as mitral stenosis and insufficiency.[3]

The aortic annulus on the other hand is rarely calcified extensively and becomes calcified mainly as a result

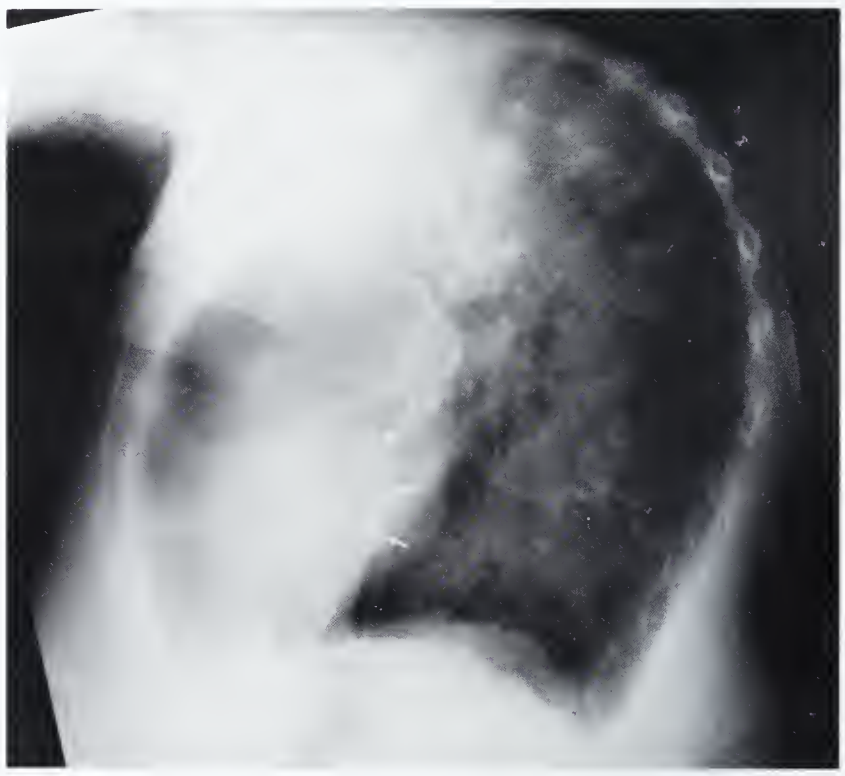


Figure 4: Calcification of the mitral valve annulus. The densely calcified annulus has a characteristic location on both views and generally has the configuration of an open circle, U or C.

of spreading valvular calcifications.

Left Atrial Calcification

Left atrial calcification is an uncommon manifestation of Rheumatic mitral valve disease and in itself is a relatively rare finding.[7] The calcification typically observed is that of a thin curvilinear sheet which follows the contour of the atrial wall, is most often located in the superior posterior aspect of the atrium, and represents calcium deposition within the endocardium or within left atrial mural thrombi (Fig. 5). The detection of left atrial calcification is an important radiologic finding. It is diagnostic of Rheumatic mitral disease and is associated with a clinical picture of predominant mitral stenosis.[3] The presence of atrial thrombi indicates a significant risk of peripheral embolization and left atrial calcification in general poses many technical difficulties to any surgical intervention.[7]

Calcification of the Coronary Arteries

Calcification in the coronary arteries is a very common finding and postmortem studies have shown cal-

cium deposits in the coronary arteries of 80% of patients over age 40. These deposits of calcium are invariably located in areas of advanced atherosclerotic disease.[8] The calcifications usually appear as plaques or double lines (Fig. 6). They are most frequently seen in the proximal arterial system within a few centimeters of the origin of the coronary vessels from the aorta. The most commonly involved vessel is the left anterior descending artery[8] lying just within the cardiac shadow on an AP view. Small deposits of calcium are often inconsequential but large, dense and extensive ones are associated with significant narrowing of the coronary arteries, impaired coronary circulation and subsequent myocardial ischemia and infarction.[3] In general, the presence of obvious calcification in a patient under the age of 50 is suggestive of clinical ischemic heart disease. Calcification can, however, be commonly seen in older patients without any clinical or subclinical symptoms.[4]

Myocardial Calcification

There are several different causes for myocardial calcification. These include rare entities such as congenital aneurysms, myocardial tuberculosis, congenital syphilis, myocarditis, and metastatic and idiopathic calcification. The most common cause of myocardial calcification is myocardial ischemia and infarction.[3] In this situation calcium is deposited in degenerate or dead myocardial tissue usually resulting from inadequate coronary blood supply. The calcification is most commonly seen in the anterior wall of the left ventricle. Occasionally, calcification can be found elsewhere including within ventricular wall aneurysms resulting

Figure 6: Coronary artery calcification. Note the parallel calcified lines extending anteriorly from the aortic root.

Figure 5: Calcified left atrium. The calcification is usually in thrombus lining the atrium.

Figure 7: Ventricular aneurysm. A thin line of myocardial calcification outlines the bulging left ventricle.

from ischemic disease. Here the calcification is deposited in a thin curvilinear layer following the contour of the aneurysm wall (Fig. 7).[2] Clinically, patients with myocardial calcification commonly suffer from ischemic heart disease and have usually survived for several years after having a large infarct.[3]

Summary

In summary, calcium deposition within the heart can be illustrated through radiographic studies. Classical anatomic positions and deposition patterns differentiate the various locations of cardiac and pericardial calcification. Each location is associated with specific etiologies and disease processes such as coronary atherosclerosis, cardiac aneurysms, pericardial disease, and valvular heart disease. Thus the clinical and pathological significance of cardiac and pericardial calcifications detected on a chest radiograph is intimately related to their anatomic localization, which is essential for the accurate assessment of such a radiograph by a physician.

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Diagnosis
Answers to Questions:

Case One

1. The differential diagnosis of painless vaginal bleeding during late T-2 - early T-3 of pregnancy is:
    1. Placentia previa (till proven otherwise).
    2. Abruptio placenta.
    3. Pelvis lesion (cervical, vaginal etc.)
    4. Vasa previa.
2. Abdominal ultrasound revealed a complete placenta previa.

Case Two

1. The ultrasound shows a snowstorm pattern in the uterine cavity and no evidence of a fetus.
2. Complete molar pregnancy.

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A Glimpse of Ethiopia

Carol Durno, 9T1

This past summer I spent three months in Ethiopia researching a project in malnutrition. This study focused on the psychosocial and familial factors that contribute to malnutrition during non-famine conditions. The first six weeks I lived in Jimma Town located in Southwestern Ethiopia (380 km south of Addis Ababa). The Jimma Institute of Health Sciences was opened in 1985. It is the nation's third medical school. The basis for building this medical school was to train physicians in a rural community so they can effectively practice in a rural hospital or health centre. Education, housing, and food are provided to all medical students at no cost. The majority of the students had been raised in an urban area so adjusting to the isolation and the rustic environment was extremely difficult. Figure 1 illustrates a rural farming family who live about one hour by foot from the Institute.

Students are slotted into specific university programs based solely on high school marks. I met a student who wanted to study business but his marks were at the medical school level. A student who turns down an offer of admission to any program is denied consideration into all other courses. As a result many students are very unhappy and dissatisfied with the career "chosen" for them.

There is a premedical year of English, Science and Marxist studies. The medical curriculum resembles that of a Canadian medical school, with two years of basic sciences followed by two years of clinical rotations and a one-year rotating internship. Severe constraints on the training of students exist because of crowded library facilities, shortages of textbooks, teaching material, and staff. Many of the Professors at the Jimma Institute were Cuban and the remainder were Ethiopian, mostly trained abroad. All of the courses were taught in English and not in the Ethiopian official language, Ahmaric.

Throughout the years of medical school there is always the risk of being "removed" from the program due to low grades or a poor attendance record. This was a tremendous stress experienced by most of the students. After failing out of a university program a student was not admitted to study again. As a consequence the students pushed themselves to a point I never thought it would be possible. They literally studied or attended classes for eighteen hours a day. Rumors of numerous scholarships available to study abroad, particularly in Canada and Russia, circulate among the students. About half of the students who do study abroad never return to Ethiopia.

My project consisted of surveying the primary caregiver in each dwelling and measuring all of the children under five years in the household to determine nutritional status. The measurements included: head circumference, mid-upper arm circumference, triceps skinfold thickness, height and weight. In figure 2 a young Ethiopian boy is being weighed during the study. The project required substantial involvement with each family so I was able to experience the Ethiopian culture and way of life. In the family studies, lack of food was not the predominant factor leading to malnutrition. The problem was the choice of food. Fresh fruits and vegetables were plentiful but not often consumed. Meat was available but was reserved for the adult males who were thought to need the protein to maintain their muscles. Many of the children were never given any protein and as a result frequently suffered from kwashiorkor (protein deficiency). In some villages the people believed developing generalized edema, dermatosis and thinning and decoloration of the hair (all characteristics of kwashiorkor) was a normal developmental stage of a growing child. The main food eaten in Ethiopia is "injera" which is a flatbread and is frequently served with a hot pepper sauce and eaten with their hands. I found it very difficult to allow someone to place food in my mouth with their hand but knowing it was a custom displaying friendship and love I felt compelled to participate. Frequently I was invited inside the hut to measure the children because the culture believes sun-

A rural farming family

light is harmful to babies (this lack of sun exposure was the cause of the severe rickets problem present in Ethiopia years ago). It was common for the people to keep their animals (cows, goats, roosters etc.) inside the one-room hut in order to provide extra body heat during the cooler seasons. Also, it was a means to prevent the animals from wandering away.

I had the opportunity to spend time in the Regional Health Center and in the Pediatric Ward of The Jimma Hospital. The Center runs numerous community programs such as Birth Control, Antenatal Care, and Nutritional Rehibilitation. Children enrolled in the Nutritional Rehabilitation Program attend a clinic once a day where they receive fafa (pablum) and have their weight recorded while the mothers have a brief Nutrition and Hygiene lesson (see figure 3). Dysentry and gastroenteritis were the most common cause of outpatient visits followed by helminthiasis and eye disease. Tuberculosis was the most common cause of hospitalization followed by gastroenteritis and pneumonia. Despite abortion being illegal in Ethiopia, complications of criminal abortions, including sepsis and renal failure, are common reasons for hospitalization. Many hospitalized patients that I examined were admitted because of injuries or secondary infections caused by "traditional healers". Many believe that diarrhea is caused by an evil spirit so the patient's skin is burned with hot knives with the hope of chasing the spirit away. Butter and cow dung are applied to the newborns severed umbilical cord which is believed to bring luck to the child. These beliefs are usually held by both the uneducated and the educated people. One fourth year medical student asked me if a pregnant woman who looked at a deformed person would bear a baby with the same deformity? This student realized that scientifically this was a ridiculous question but this was a widely accepted cultural belief. It is difficult to understand how these harmful beliefs could remain part of a culture for generations.

Nutritional rehabilitation program at health center

Malnutrition project - measurements

Today when looking back at my summer in Ethiopia I find it all hard to believe. The medical students are preparing for the challenges that await them; working in a rural community as the only physician for up to three hundred thousand people, with an undersupply of drugs, and few or no vehicles to serve their vast area of service coverage. Many of these students are optimistic that this situation will improve.

The Medical Manager

Software Reviewed by
Ian Y. Pun, 9T0, Paul Wong, 9T0

Publisher: Systems Plus, Inc., 500 Clyde Avenue, Mt. View, CA 94043, (916) 969-7047

Description: Comprehensive software package for medical office management, including patient records, billing, accounting and report generation; can be customized to fit user's needs; menu-driven user-friendliness; an extremely powerful and complex program. Version 5.2 (with Office Management and Electronic Medical Claims options)

Hardware requirements: IBM PC/XT/AT or compatible computer, 640K RAM, at least 2 MB of hard disk space, monochrome or colour monitor, any 132 column printer, MS-DOS 3.3. Optional multi-user LAN version available. Also available for other micro or mini-computers running CP/M, MP/M and UNIX operating systems.

Cost: $3,500-$10,000 U.S. depending upon user's options; seminar training is available.

MEDICAL MANAGER is a database package aimed at automating a medical office. The system is designed mainly for multi-physician practices but it can be easily adapted to single practices. It is very comprehensive and versatile in its functions which range from administrative, correspondence, clinical and financial aspects of a busy practice. Patient records can be stored and billing can be instituted and with an optional package, Electronic Medical Claims, Due to the program's complexity, customizing the database to one's own needs requires a detailed knowledge of general computer concepts and technical aspects of the program; therefore, extra support from computer consultants may be necessary to initially implement this system. The package we received (version 5.2) contained nine 360K floppy disks, one thick 500-page operator manual and a 300-page technical manual. Due to space limitation, this review only encompasses major points of the program.

Installation

Installing and configuring the program was tedious, requiring a little bit of knowledge of the MS-DOS operating system. The software must be configured to the type of video display, terminal, and function key definitions. Because of the program's ability to customize or adapt to different computer systems, installation could take one half to two hours and may require outside expertise. A ready-to-run version or at least an automatic installation program could prevent some frustrations a new user may have.

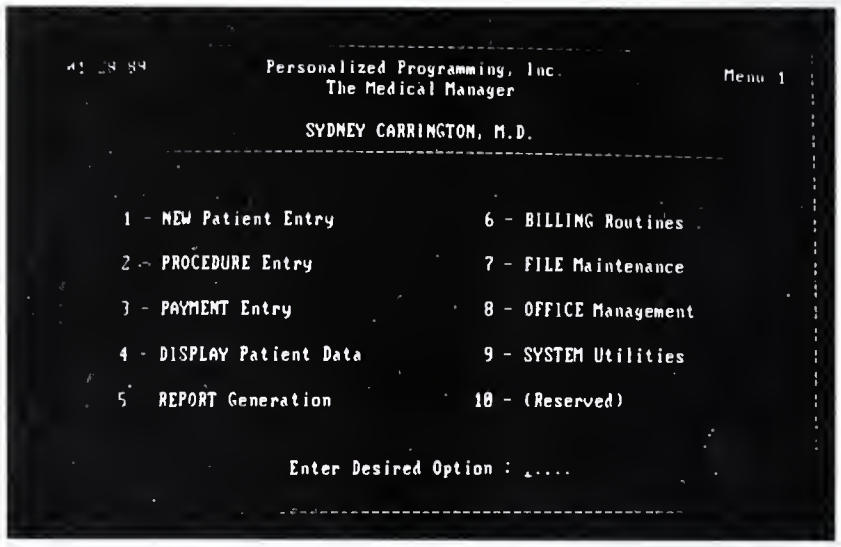


Figure 1: The Main Menu

Before entering the system, one must enter the user number (MEDICAL MANAGER accommodates up to 40 different users) and the password. Different users have different security access levels; only the level 1 user may modify the system while a level 9 may enter and only read existing data. Upon entering the system, you are greeted by a general system menu from which all the functions are choosen. (see fig. 1). Each option has two to three deeper sub-menus as well.

Patient Data Management

The types of data that can be entered and stored include patient general information (name, sex, age, address, ...etc.), procedures and payment. Payment entry is for posting payments, adjustments and refunds into a patient's account according to a pre-existing individualized pay schedule that may be modified as required. Extensive use of defaults, on-line help and excellent error-checking makes it an easy task to enter information. Procedures are entered as codes similar to OHIP (it can be changed to OHIP format) and these codes can be called up for reference. We were pleased with the program's high degree of error-trapping at the data input level, that is, the operator could not enter invalid data whenever a specific format is requested (i.e., a number when a name is expected) for example entering "1234567" will reformat as "123-4567" if it is a telephone number. This feature prevents nonsense data in being entered which would have otherwise confused the system and its users. The program continuously checks its data for errors and keeps a log so that files could be revived by a file rebuilding utility should corruption were to occur due to hardware problems.

We feel that a competent secretary could learn the data entry procedure in a matter of hours. But like all computerized office systems, there is a major overhead in manually entering information into a computer On the other hand, a new practice may benefit from the

future potentials of an automated "paperless" office. The physician may enter the data himself or dictate it to the secretary.

Office Information Management

The Appointment Scheduling is quite complete and useful. You may schedule specific patient's appointments to specific doctors or clinic room numbers and search a patient's previous or next appointments. Number of time slots and description of reason for the appointment is allocated to each patient. The daily appointment schedule could be printed out for one or more physicians. Also, a patient's total history of appointments can also be printed out, which is useful for following patient compliance. Recall notices can also be printed and sent to patients.

Pertinent information of a specific patient can be searched for clinical, procedural, diagnostic and financial history, given useful past medical health history. For example, clinical history displays drug, allergies, childhood disease, family diseases, previous illnesses and other surgical histories of the patient.

Frequencies of certain procedures and their corresponding revenues can be reported. This information is meaningful in testing the productivity of the existing resources within the practice. Hospital Rounds reports patients status within hospital and helps in scheduling and billing for hospital rounds for different physicians.

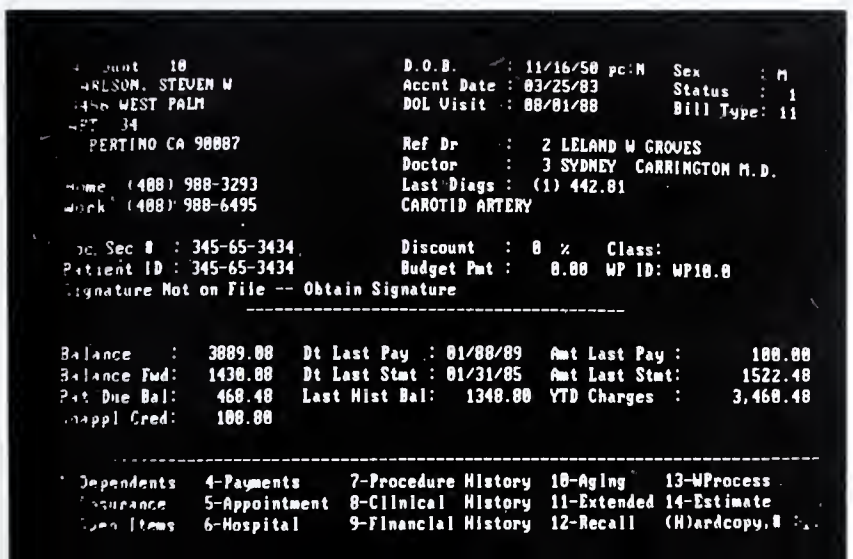
Correspondence

Comprehensive functions for all aspects of a medical practice's billing needs and communications are provided. These include routines to handle billing forms and formats, patient billing and statements, insurance billing and outstanding balance follow-up. Correspondence of gratitude to referring doctors and reminders to patients for their appointments can be automated.

Financial Management

The Billing routines are for the generation of bills and statements to be sent to the guarantor and their respective insurance companies. The MEDICAL MANAGER permits an unlimited variety of billing styles in order to meet the requirements of different medical practices and insurance companies due to the ability to generate custom forms, a tedious task requiring a fair bit of computer knowledge. Since this program was written for use in the United States, Canadian insurance such as OHIP may require these custom forms and extra support from the publisher or consultants. Insurance claims can also be submitted electronically on floppy disk or modem as protocol text files, through the optional Electronic Media Claims module. Again, the OHIP protocol must be included for use in Ontario. Display Patient Data accesses every piece of account data without printing a lengthy report as well as clinical and treatment history of the patient (see fig. 2).

Figure 2: Guarantor information input screen


D.O.B. : 11/16/50 pc:M Sex : M
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DOL Visit : 08/01/88 Bill Type: 11
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Balance Fwd: 1430.00 Dt Last Stmt : 01/31/85 Amt Last Stmt: 1522.48
Pat Due Bal: 460.48 Last Hist Bal: 1340.00 YTD Charges : 3,460.48
Unappl Cred: 100.00
3-Dependents 4-Payments 7-Procedure History 10-Aging 13-WProcess
5-Appointment 8-Clinical History 11-Extended 14-Estimate
6-Hospital 9-Financial History 12-Recall (H)ardcopy,0

Documentation

Two thick manuals accompany the system. The operator manual teaches you step-by-step, the complete commands and data entry in tutorial form, following each detail of the system. An added short glossary of the commands would have been more useful for users who would not have the time to go through a time-consuming tutorial and just simply want to play with the system first. The technical manual, which describes the fundamental data formats and structures of this database, is an added bonus for an expert user or programmer but is beyond the scope of the normal user, that is, the average physician. Unfortunately, if you wish to define your personal OHIP billing forms, for example, you would need to learn these data formats in order to produce custom forms. Obviously, without advanced computer knowledge, consultants will be necessary.

Performance

We evaluated MEDICAL MANAGER on a 12 MHz IBM AT compatible computer with a 40 ms hard disk drive. Generally, the program performed smoothly since loading different modules took one to two seconds. Searching through patients is nearly instantaneous due to its internal B-tree data structure, an advanced computer science technique which requires no re-sorting time. Although we only had a small patient database (only 20 patients), we would expect a large patient population (over 1000) would not considerably slow down the searching functions. Help menus and report generation were instantaneous. Although the system is relatively easy to use, it was easy to be lost in the complex menu structure hierarchy. An indication of your location would have been useful. You can exit any function at any time by pressing the escape key which is an excellent feature.

In conclusion, MEDICAL MANAGER is a very capable program in managing an office. Its complexity of intitial implementation may turn away prospective users since this package pertains only to the American health care system. Using the system in Ontario would require a set of custom OHIP billing forms and procedures. But once installed, the program is a very easy to use and had great potential. MEDICAL MANAGER is unquestionably one of the most powerful management programs on the market. However, this high power comes with a high price. The $3,500 price tag for the basic program may not be justified for a single physician practice since many features pertain to a multi-physician setting.

Cochlear Implants: Effective Treatment for Profound Sensorineural Hearing Loss

Henry L. Woo, 9T0

It has been over three decades since the first attempts at cochlear implants were performed. To date, more than 2500 patients worldwide have received some type of implant. Cochlear implant technology has expanded rapidly over the past several years.

In simple terms, the cochlear implant is a prosthesis which effectively bypasses the entire mechanical transducer system of the ear, including the cochlear hair cells, and thus makes possible direct electrical stimulation of the auditory nerve itself. There are a variety of different systems in use, but all have similar components including: a microphone to receive sound; a speech processor for converting the acoustic energy into electrical signals; a transmission system to deliver the signal; and implanted electrodes to deliver the electrical stimuli to the auditory nerve fibres.

The most common site for implantation is intracochlear, where the stimulating electrodes are surgically passed through the round window and into the scala tympani of the cochlea. The electrodes extend approximately one full turn within the cochlea. Other less favoured sites for electrode placement include the promontory and round window within the middle ear cavity adjacent to the cochlea. A very exciting possibility is presently being explored, namely that for electrode placement directly on the brain stem such that stimulation of the cochlear nucleus itself occurs.

Patient selection is based upon a complete audiological assessment, evaluation of communication skills, lipreading ability, language comprehension and the patient's general expectations of implantation. The latter is to provide the patient with realistic goals of treatment, those being: environmental sound awareness, better self-regulation of one's voice, improved lipreading ability, and an increased overall sense of safety and well-being.

Cochlear implants are appropriate in patients with profound bilateral sensorineural hearing loss due to inner ear hair cell pathology without impaired function of the remainder of the auditory pathway. Some common etiologies of hearing loss seen in implanted patients include hereditary causes, meningitis, Meniere's disease, ototoxic drugs, labyrinthitis, otosclerosis and idiopathic sudden sensorineural hearing loss.

Patients who have acquired language skills before the onset of their hearing loss appear to receive the most benefit from the cochlear implants. Those with congenital hearing loss have not fared as well, mainly due to their underdeveloped ability to process the signals as effectively. Some implanted patients have consistently achieved word discrimination scores of above 80% correct. In addition, patients previously suffering from tinnitus or vertigo have reported either improvement or at least no change in their symptoms with implantation.

Although the current devices are still far from ideal, the ability to provide hearing sensation to those with primary cochlear hair cell disease is no longer in question. As technology advances further, the continued application of cochlear implants appears promising.

Human Bone Marrow Cells Transplanted into Mice

Zeke Milkovic, M.Sc., 9T0

Researchers at the Hospital for Sick Children in Toronto have successfully transplanted human hematopoietic stem cells into mice. Kamel-Reid and Dick (Science 242: 1706-9, Dec. 1988) have taken the work of U.S. researchers one step further by reconstituting both the lymphoid and myeloid human lineages in the mouse. McCune et al. (Science 241: 1632-9, Sept. 1988) and Mosier et al. (Nature 335: 256, 1988) have been successful at transplanting human fetal lymphoid cells into mice.

A special strain of mice was bred called human immune-deficient mice (HID). Three genetic mutations rendered the mice athymic, with reduced numbers of natural killer (NK) cells and lymphokine activated killer (LAK) cells. As well, the mice were irradiated. Human bone marrow cells were injected intravenously into the mice. After 14 days, DNA from the bone marrow and spleen was analyzed by Southern blot technique to quantitate the proportion of human cells in the hematopoietic tissues of the recipient. It was found that human DNA was present in the bone marrow and spleen of the animals. It was also determined that exogenously applied human growth factor was not necessary for growth. This suggested that the human stem cells were producing their own growth factors or responding to mouse growth factors or both. A rapid rate of growth of stem cells was observed for a period greater than five weeks. The findings of this study are significant because the HID mice will be a valuable model in which to test gene transfer and longterm expression in human hematopoietic cells. In addition to gene therapy, the HID mice may be an important system to develop models of human leukemia, sickle cell anemia and thalassemia; to develop assays for growth factors and chemotherapeutic agents; and finally, for the study of acquired immunodeficiency syndrome.

Radiosurgery: Alternative to Microsurgery for Small Intracranial Lesions

Zeke Milkovic, M.Sc., 9T0

Stereotactic radiosurgery using a gamma knife is proving to be a valuable alternative to microsurgery for removing small intracranial lesions. Pittsburgh researchers, as reported in The Medical Post (Vol. 24, no. 40, Nov. 8, 1988) have used it mainly to treat benign tumors, as well as additional therapy in a few malignant tumors.

The gamma unit uses 201 cobalt-60 sources to produce an array of highly focused narrow beams converging at a point to deliver a single, precisely targeted high dose of radiation.

The gamma knife has been used to treat patients with lesions deemed unresectable or incompletely resected following previous surgery. The majority of lesions treated were arteriovenous malformations (AVMs). The preliminary results are encouraging for AVMs but are still being assessed for lesions such as acoustic neuromas, meningiomas, and pituitary adenomas. Total obliteration of the AVM at the end of 1 year of treatment occurred in about 50% of patients, 84% at the end of 2 years and over 90% by the end of the third year. In 3% of the AVM treated patients, complications such as new neurological deficits and radionecrosis occurred.

Radiosurgery by the gamma unit has reduced the average stay in hospital and has reduced treatment costs significantly as well. The majority of the patients are discharged within 24 hours of treatment.

An advantage of the gamma unit is that the dose can be tailored to accurately correspond to the irregular margins of tumors. This high precision dose contributes to the safety and efficiency of the treatment.

The disadvantage of the unit is the cost — $3 million for the 20-ton piece of equipment. Furthermore, the expertise of a large team of professionals including neurosurgeons, radiation oncologists and physicists and support staff is required to run it. Thus, availability of the gamma knife will be limited to major medical centres.

Head and Neck Surgery

Michael J. Weinberg MSc, 9T0, Ralph T. Manktelow, Ronald M. Zuker, Brian Boyd and Irving B. Rosen MD D

Major advances have been made in the field of head and neck surgery, in terms of survival and cosmesis. The primary treatment of oral carcinoma is frequently radiation although primary surgical treatment is being more frequently utilized. Surgery is used for the treatment of radiation failures or recurrences. Thus, surgery offers such patients their only chance of survival. However, life-saving surgery can produce loss of tissues that may leave the patient mutilated, and with dysfunctional deformities. Current thinking in cancer treatment stresses that, if at all preventable, deformity and dysfunction are no longer acceptable exchanges for successful cancer treatment.

The surgical team involved usually consists of a combination of plastic surgeons, otolaryngologists and head and neck surgeons. The Toronto program has pioneered many of the techniques in this field and has one of the largest experiences in the world. Microvascular repair following ablative head and neck cancer surgery serves this purpose. Many donor sites are available for microvascular reconstruction and they include the iliac crest osteocutaneous flap, the dorsalis pedis second metatarsal osteocutaneous flap and the osteocutaneous forearm radial flap.

The new techniques in microvascular reconstructive surgery have benefited patients tremendously. First, the techniques have greatly improved function such as speech and oral continence. Second, the cosmetic effects are superb, allowing the patients to continue their normal lives instead of living with constant shame. Finally, since the cosmetic results are so good, the ablative surgeon can be much more aggressive in obtaining cancer-free wider margins in excision of the primary, which promotes improved survival.

A B

*Panel A: Preoperative appearance of a man with advanced cancer involving the floor of the mouth, mandible, and facial skin. Panel B: Postoperative view after resection and reconstruction with an osteocutaneous iliac crest flap. The flap provided both an external and internal lining of the mouth and mandibular replacement. The patient was alive and free of disease 1 year postoperatively. The man was a patient of Dr. Brian Boyd of the TGH.
*Figures reproduced from Am.J.Surg. 1985;150:474-479.

BOOK REVIEWS

Essentials of General Surgery

edited by Peter F. Lawrence
Williams and Wilkins, 1988, 410 pages

Well, we have books — and of course more books — and then there are seminars and syllabus notes, and lecturers rarely adhere to the syllabus, and then we have clinic notes. It seems like a mad scramble to fit everyone's little contribution together. It is thus often frustrating for the medical student to piece it all together, not to mention trying to sort out what is important. Wouldn't it be comforting and wouldn't it optimize learning to have it all in one place, or at least integrated at the correct level? Yes, it can be done and has been done with the multi-media package for surgical clerkships. The text Essentials of General Surgery is part of this integrated package that is designed to convey the required information to surgical clerks. The package includes a text to teach surgical knowledge, videotapes to teach surgical procedures and skills, computer problems to teach clinical decision-making, a bank of examinations (both oral and written) to test the information that has been learned and a set of 35 mm slides. I should mention that all these modalities are going to be made available to students as well as to staff. The text will, as of next year, become the recommended text for surgery.

I will just comment on the text. There are 28 chapters. The first 5 chapters (107 pages) offer some basic knowledge and background information on surgery. These are most helpful and very practical especially the chapter on health care issues, surgical record keeping, the O.R. and surgical procedures for students. Chapters 5 to 10 deal with basic surgical principles and problems such as shock. The remaining chapters are arranged by organ system and basically cover general surgery, although there are chapters on malignant diseases of the skin, lymphatics and soft tissue. Each chapter has a characteristic structure. There are assumptions (i.e. what does the clerk already know.), extensive objectives, the subject matter, list of skills required, study questions and suggested readings. Thus, this is a nice complete package that makes for more efficient learning. The chapters contain the information that a clerk or third year student should know. It stresses concepts such as pathophysiology, treatment (medical and surgical) and outcomes of common surgical disorders. Obscure details and diseases are omitted. The emphasis is on concept and understanding. This book is easy to read and not so long that it cannot be read in third year and again in clerkship. If it is used in the multimedia package, I think that this is going to be a very powerful learning tool. There were, however, some problems. First, I think the book was very wordy. There could have been many more tables and diagrams summarizing the important points. Second, there could have been more point form, such as that used in current surgical diagnosis and treatment, edited by L.W. Way. Finally, a chapter on the basic approach to surgical problems and abdominal symptoms is conspicuously lacking.

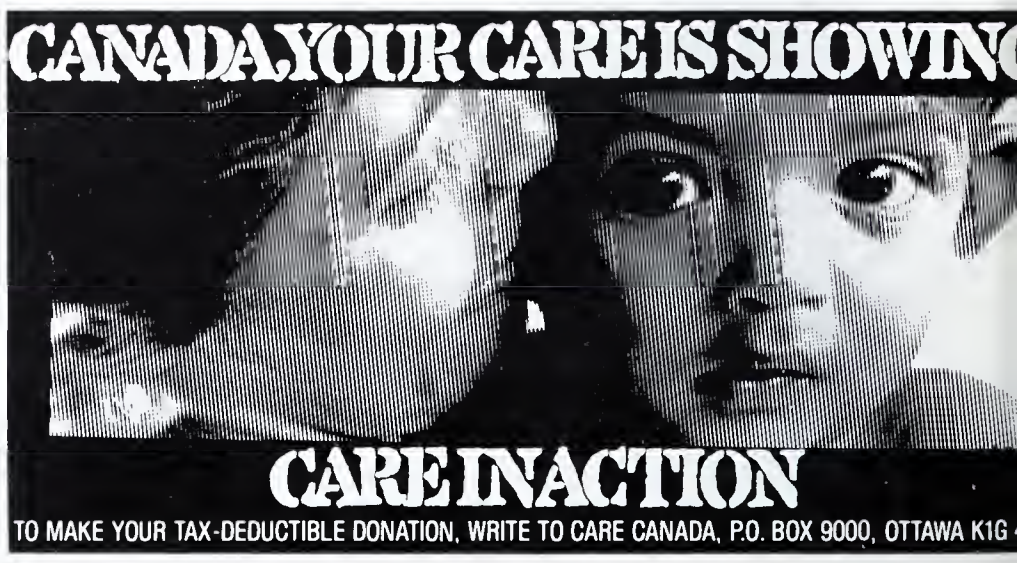
Michael J. Weinberg, M.Sc., 9T0

Fluid, Electrolyte, and Acid-Base Emergencies

by Halperin and Goldstein
W.B. Saunders, 354 pages

This is not one of those "The Essentials of ..." books. It is a book that is all meat and no filler and it ought to come with a warning that only those readers who have a good understanding of basic physiology should attempt this book. I say, "attempt", because one does not read this book in the common, sequential way, one page after another. This book is not written that way. It is written in a guerilla warfare style: A blast here, an announcement there, a "pearl" somewhere else. This style makes first-time learning difficult, but the reader who knows the basics rejoices at the directness and compactness of the information. Each topic is introduced via the Halperin trademark, The Big Picture and each topic comes with pages of "sidelights" that may be illustrative clinical cases on specific examples of the topic under consideration. The book does not present simply a list of things to do under the circumstances. Instead, it explains fluid, electrolyte and acid-base disorders in terms of fundamental concepts and, thereby enriches the reader's understanding of this complex area. This book will not make the Renal Electrolyte section in the first year physiology course any easier, but I regard it as an indispensable reference text for what lies beyond first year.

U. Ackermann, Ph.D.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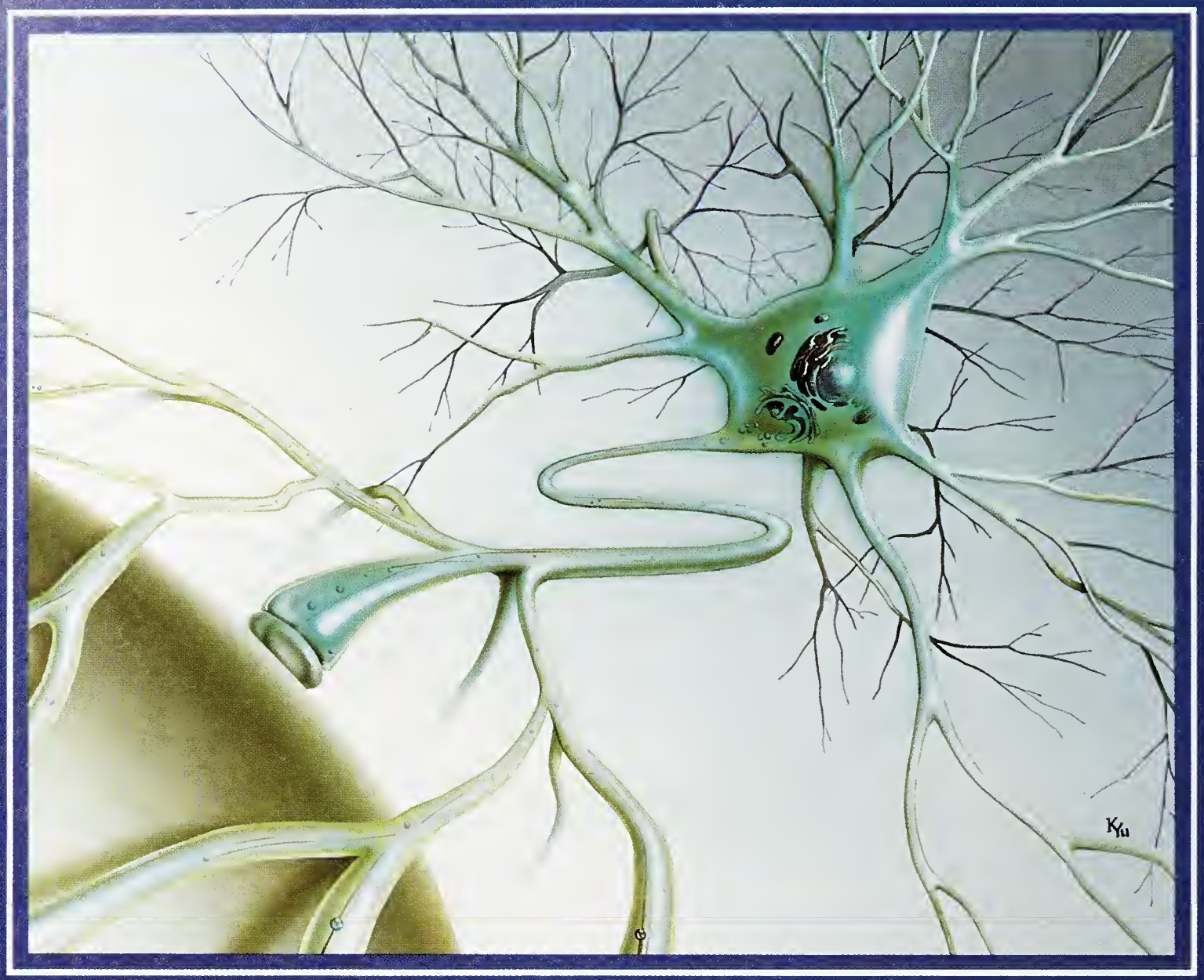

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